# A Culture of Quality? Lymph Node Evaluation for Colon Cancer Care

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

Helen Mari Parsons

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Beth A. Virnig, PhD, MPH
Advisor

December 2011

**Acknowledgements**

I would like to thank my family, friends, and dissertation committee for their incredible support and encouragement throughout the process of writing this dissertation. Without their continued feedback and insight, completing my dissertation would not have been possible.

## Abstract

Colon cancer care provides an important opportunity to identify how providers and policymakers can achieve high quality outcomes in the context of quality guidelines. Among patients surgically treated for colon cancer, better survival has been demonstrated in those with more lymph nodes evaluated. Evaluated at the time of surgery, lymph node involvement (i.e. node positive disease) indicates advanced disease among colon cancer patients and a recommendation for adjuvant chemotherapy. Over the past 20 years, several practice organizations and consensus panels have identified the surgical evaluation of 12 or more lymph nodes as an important quality indicator for appropriate staging and treatment of newly diagnosed colon cancer patients. However, the exact mechanism behind more extensive lymph node evaluation and improved survival remains contentious. Using the Surveillance, Epidemiology and End Results (SEER) data and the SEER-Medicare data, which combines a set of cancer registry data linked to Medicare administrative claims, this research evaluates current gaps in knowledge surrounding the achievement and impact of lymph node quality guidelines for colon cancer care by l) further evaluating the mechanism between lymph node evaluation and survival 2) identifying whether high quality comprehensive care might account for this relationship and 3) understanding how to significantly improve guideline adherence among providers of colon cancer care. Overall, this research provides timely evidence for future guideline recommendations surrounding the relative impact of lymph node evaluation for colon cancer care.

## Table of Contents

## List of Tables

## List of Figures

## List of Appendices

**Chapter 1: Specific Aims**

With over 100,000 new colon cancer cases diagnosed in the United States each year,[1] identifying pathways for improved survival and treatment is critical for reducing the burden of the disease on the population.[2] Among patients undergoing surgery for colon cancer, better survival has been demonstrated in those who have more lymph nodes evaluated.[3-7] Lymph node involvement indicates more advanced disease and a recommendation for adjuvant chemotherapy after surgery.[8-10] As a result, several practice organizations and consensus panels have recommended the surgical evaluation of 12 or more lymph nodes to facilitate adequate staging and appropriate treatment for colon cancer over the past 20 years.[11-14] Initially, the primary mechanism for this association was believed to be upstaging, where a more extensive evaluation of lymph nodes resulted in more accurate determination of nodal status. However, studies have demonstrated that higher lymph node counts did not necessarily result in a shift towards higher staged colon cancers.[15-17] Rather, higher lymph node counts led to improved survival regardless of whether they were node positive or negative.[18-19] Recently, several groups have advocated two alternative hypotheses. First, this relationship may result from an improvement in surgical quality and treatment. More experienced, higher volume surgeons and facilities may perform quality procedures, evaluating an increased number of nodes in the process.[15, 20-21] These patients may additionally receive more appropriate adjuvant therapy for their disease, as well as better follow-up care. Alternatively, the lymph node-survival relationship may reflect an underlying interaction between the tumor and individual, influencing survival.[22] In other words, tumor factors may stimulate lymph nodes to enlarge, reflecting immune system recognition of the tumor and more favorable survival outcomes. To date, the literature lacks a consensus on the driving force behind the lymph node-survival relationship.

In order to further understand the relationship between quality, biology and colon cancer outcomes, I will use Surveillance, Epidemiology and End Results (SEER) data and the SEER-

Medicare linked data to identify how this relationship has evolved with the institution of quality guidelines over the past 20 years. If quality is the predominate force in this relationship, we should see a relationship between guideline recommended lymph node evaluation and other markers of high quality care that drive survival. Therefore, the specific aims of my proposed research are to:

**Specific Aims**

1. Examine the association between more extensive lymph node evaluation, identification of lymph node positive cancers and hazard of death over the past 20 years.

2. Examine whether people receiving adequate lymph node evaluation (≥12 nodes examined) are also more likely to receive more comprehensive post-surgical care, leading to lower mortality.

3. Determine hospital characteristics associated with improvement or maintenance of guideline-recommended lymph node evaluation after the first published guidelines in 1990.

Understanding the mechanism that influences the node-survival relationship and leads to improved adherence to guideline recommended care will be instrumental in the design of future quality improvement programs. While lymph node evaluation alone may not drive improved survival, understanding the best combined mechanisms for influencing guideline recommended care will be important for identifying those components that significantly improve the quality of colon cancer care in the US.

**Chapter 2: Statement of Purpose and Background**

Over the past decades, the development of quality guidelines for best-practice medical care has become a priority for policy makers, payers and health care providers.[23-24] However, the Institute of Medicine continues to identify significant gaps between knowledge and practice for health care delivery.[23] With the growing complexity of care combined with an aging population, the US healthcare system will require specific mechanisms for identifying how high quality care can be achieved. In the context of wide-ranging quality improvement efforts in medical care,[25] optimizing cancer care through accurate staging and appropriate treatment has become an area of substantial interest to policy makers as it identifies appropriate therapeutic decision-making and prognostic estimates.[23-25]

Colon cancer care provides an important opportunity to identify how providers and policymakers can achieve high quality outcomes in the context of quality guidelines. Over the past 20 years, several practice groups and consensus panels including one convened by the National Cancer Institute identified the surgical evaluation of 12 or more lymph nodes as an important quality indicator for appropriate staging of newly diagnosed colon cancer patients.[13-14, 26] Among patients surgically treated for colon cancer, better survival has been demonstrated in those with more lymph nodes evaluated.[6] Lymph node involvement indicates advanced disease among colon cancer patients and a recommendation for adjuvant chemotherapy.[8-10]

In the context of rising healthcare costs, identifying and treating those patients most likely to benefit from adjuvant therapy remains an import goal; particularly when over 104.1 billion dollars are spent each year in the US on cancer care alone.[27] In the near future, cancer care costs may actually increase at a faster rate than general medical expenditures. Therefore, understanding where to focus quality guidelines remains important for influencing both cancer outcomes and rising healthcare costs. However, significant criticisms have emerged regarding the suitability of the lymph node evaluation guideline to significantly improve survival and outcomes

in colon cancer patients. Initially, the primary mechanism for this association was believed to be upstaging. In other words, a more extensive evaluation of lymph nodes resulted in more accurate determination of nodal status. However, studies from large multicenter institutions and population based analyses have demonstrated that higher lymph node counts did not result in a shift towards higher staged colon cancers.[16-17] Rather, higher lymph node counts resulted in improved survival regardless of whether they were node positive or negative.[17-18]

Recently, several groups have criticized the proposed mechanism between nodal evaluation and survival, advocating two alternative hypotheses.[16, 22] First, this relationship may result from an improvement in surgical quality and treatment. More experienced, higher volume surgeons and facilities may perform higher quality procedures, evaluating an increased number of nodes in the process. Additionally, these patients may receive more appropriate adjuvant therapy for their disease and more comprehensive follow-up care. Second, this relationship between nodes evaluated and survival may reflect an underlying interaction between the tumor and individual, influencing survival.[22] In other words, tumor factors may stimulate lymph nodes to enlarge, reflecting immune system recognition of the tumor and more favorable survival outcomes.

In order to further understand the relationship between quality, biology and cancer outcomes, several studies have examined predictors of adequate lymph node evaluation and their impact on survival. In these studies, patient, surgeon and hospital characteristics all emerge as significant predictors of both nodal evaluation and cancer-specific survival, indicating that both biology and quality may drive survival outcomes.[21, 28] Further, a study by Nathan et al.[21] identified that high performing hospitals (i.e. those evaluating $\geq$12 nodes on average) were more likely to have board certified colon surgeons conducting the operation and participate in cooperative cancer groups, both indicators of specialized experience and dedicated cancer resources. Further, they found that after accounting for patient demographics and tumor

characteristics, the majority of modifiable variation in guideline-recommended evaluation occurs at the hospital level.[21] These results point towards institutional quality as an important driver of guideline adherence and outcomes. However, in 2002, over 60% of hospitals were still performing below guideline recommendations for lymph node evaluation, five years after they were published.[28]

If quality is indeed the driving mechanism between lymph node evaluation and survival, hospitals and providers then need concrete recommendations for how they can continue to improve quality and influence their colon cancer outcomes. First, further understanding the mechanism that influences the node-survival relationship will be instrumental in the design of future quality improvement programs. Growing evidence suggests that lymph node evaluation alone does not drive improved survival.[16, 22] Rather, it may be the combination of good quality surgical care with better access to adjuvant therapy. Second, identifying specific changes in hospital organization, specialty membership or physician composition will be important to identify those components that significantly influence quality of colon cancer care in the US. Currently, literature on lymph node evaluation focuses predominately on predictors of adequate lymph node evaluation- not on predictors of improvement in lymph node evaluation. Such an analysis will provide specific recommendations for improving quality measures for colon cancer care.

Overall, the proposed research will evaluate current gaps in knowledge surrounding the achievement and impact of lymph node quality guidelines for colon cancer care by 1) further evaluating the mechanism between lymph node evaluation and survival 2) identifying whether high quality comprehensive care might account for this relationship and 3) understanding how to significantly improve guideline adherence among providers of colon cancer care. The current lack of consensus on where to focus quality improvement efforts in the context of colon cancer

suggests that the proposed research will provide timely and significant evidence for future guideline recommendations.

***Relationship between Lymph Node Evaluation for Colon Cancer and Survival***

Current literature on the relationship between lymph node evaluation and survival indicates that the number of lymph nodes evaluated after surgical resection is positively associated with survival in patients with stage II (lymph node negative) and stage III (lymph node positive) colon cancers. A systematic review by Chang et al. identified seventeen retrospective studies evaluating the relationship between lymph node evaluation and survival (Table 1).[6] Although methodologies were variable, all but one study found an association between having an increased number of lymph nodes evaluated and improved survival in patient with both node positive and node negative disease.

**Table 1: Studies evaluating the association between lymph node evaluation and survival**

| Population | Stage | Study Design | Comparison | Outcomes | Timing | Study |
|---|---|---|---|---|---|---|
| 3,322 colon cancer patients who underwent complete resection of the primary tumor | II and III | Retrospective Nested Cohort | 10-year OS, CSS | Stage II<br>75% overall survival with 11-20 nodes examined, 59% <11 nodes, p<0.001<br><br>*Stage IIIB*<br><br>>64% overall survival with 11-40 nodes examined, 56% <11 nodes, p<0.001 | 1988-97 | Le Voyer [3] |

| **Table 1 (Continued)** | | | | | | |
|---|---|---|---|---|---|---|
| Population | Stage | Study Design | Comparison | Outcomes | Timing | Study |
| 3,648 colon cancer patients who underwent complete resection of the primary tumor | II and III | Retrospective Nested Cohort | 5-year OS; DFS | >76% overall survival with ≥12 nodes examined, 69% <11 nodes, p<0.0097 in stage II and III | 1995 with a median follow-up of 3.6 years | Prandi[29] |
| 35,787 prospectively collected cases of T3N0MO colon cancer, surgically treated | II | Prospective cohort study | 5-year OS | 64% if 1-2 lymph nodes evaluated to 86% if >25 nodes evaluated, p<0.001 | 1985-1991 | Swanson[7] |
| 960 randomly selected colon cancer patients who underwent major colon resection in the Ontario Cancer Registry | I, II, and III | Retrospective cohort study | OS | HR 0.6 (0.4, 1.0) in node negative patients with 10-36 nodes evaluated vs. 1-3, p=0.03 | 1991-1993 | Bui[4] |
| 2437 colon cancer patients from the Kentucky Cancer Registry | II and III | Retrospective cohort study | OS | 56% if <12 lymph nodes evaluated vs. 63% if >12 evaluated, p<0.001 | N/A | Carloss[30] |
| 8574 colon cancer patients from SEER cancer registries | II | Retrospective cohort study | 5 and 10 year OS | HR: 0.98 (0.97, 0.98) for each additional lymph node evaluated, p<0.01 | 1988-1998 | Cserni[31] |

| **Table 1 (Continued)** | | | | | | |
|---|---|---|---|---|---|---|
| Population | Stage | Study Design | Comparison | Outcomes | Timing | Study |
| 3735 colon cancer patients from the Uppsala cancer registry | II and III | Retrospective cohort study | 5 year OS | 65% if <11 lymph nodes evaluated vs. 75% if ≥11 evaluated, p<0.001 | 1997-2002 | Jestin[32] |
| 745 colon cancer patients diagnosed in a single institution | II | Retrospective cohort study | 5 year OS | 62% if <7 lymph nodes evaluated vs. 76% if ≥18 evaluated, p<0.018 | 1955-2000 | Goldstein[33] |
| 480 colon cancer patients diagnosed in a single institution | II | Retrospective cohort study | 5 year OS | 51% if <10 lymph nodes evaluated vs. 71% if ≥19 evaluated, p<0.045 | 1980-2000 | Sarli[34] |
| 222 colon cancer patients diagnosed in a single institution | II | Retrospective cohort study | 5 year OS | 49% if <7 lymph nodes evaluated vs. 68% if ≥7evaluated, p<0.001 | 1985-1990 | Caplin[35] |
| 140 colon cancer patients diagnosed in a single institution | II | Retrospective cohort study | 5 year OS | 62% if <7 lymph nodes evaluated vs. 86% if ≥7evaluated, p<0.03 | 1988-1995 | Cianchi[36] |
| 179 colon cancer patients diagnosed in a single institution | II and III | Retrospective cohort study | 5 year OS | *Stage II* 72% if <9 lymph nodes evaluated vs. 85% if ≥9evaluated, p<0.35<br><br>*Stage III* 55% if <9 lymph nodes evaluated vs. 78% if ≥9 evaluated, p<0.01 | 1997-2003 | Gumus[37] |

| **Table 1 (Continued)** | | | | | | |
|---|---|---|---|---|---|---|
| Population | Stage | Study Design | Comparison | Outcomes | Timing | Study |
| 115 colon cancer patients diagnosed in a single institution | II | Retrospective cohort study | 5 year OS | 62% if <7 lymph nodes evaluated vs. 86% if ≥7 evaluated, p<0.03 | 1994-1999 | Law[38] |
| 487 colon cancer patients diagnosed in a single institution | I, II, III | Retrospective cohort study | 5 year OS | *Stage I- II* 83% if <11 lymph nodes evaluated vs. 91% if ≥29 evaluated, p<0.35<br><br>*Stage III* 59% if <11 lymph nodes evaluated vs. 84% if ≥29 evaluated, p<0.01 | 1981-1996 | Ratto[39] |
| 487 colon cancer patients diagnosed in a single institution | II | Retrospective cohort study | 5 year OS | Statistically significant improvement in survival with ≥14 lymph nodes evaluated versus <14, exact survival rates not reported | 1995-1999 | Wong[40] |
| 94 colon cancer patients diagnosed in a single institution | II | Retrospective cohort study | 5 year OS | 49% if <7 lymph nodes evaluated vs. 68% if ≥7 evaluated, p<0.001 | | Yoshimatsu[41] |

* OS: Overall Survival; CSS: Cancer Specific Survival; DFS: Disease Free Survival; HR: Hazard Ratio

***Potential Confounders of the Lymph Node Evaluation-Survival Relationship***

*Patient Factors*

Each of the observational studies (Table 1) examining the relationship between lymph nodes and survival adjusts for differing combinations of patient, surgeon and hospital factors that might influence the relationship between lymph node evaluation and outcomes. For patient factors, these studies most often adjusted for patient age, gender, race, extent of disease, and adjuvant therapy (Table 2). However, these previous studies evaluated the relationship between lymph node evaluation and survival in select groups, which are based on single-institution findings, limited to the elderly or evaluated in patients diagnosed with specific AJCC stages. As a result, these studies may not fully capture the true relationship between nodal evaluation and survival when the association is evaluated in a large population-based sample of all surgically-treated colon cancer patients.

**Table 2: Patient confounders included in studies evaluating the relationship between lymph node evaluation and survival**

| Study | Age | Gender | Co-morbidity | Histology / Grade | Extent of disease | Socio-economic status | Insurance | Adjuvant Therapy |
|---|---|---|---|---|---|---|---|---|
| Le Voyer[3] | X | X | | X | X | | | X |
| Prandi[29] | X | X | | X | X | | | |
| Swanson[7] | X | | | X | | | | X |
| Bui[4] | X | X | X | X | X | | | |
| Carloss[30] | N/A | | | | | | | |
| Cserni[31] | X | X | | X | X | | | X |
| Jestin[32] | X | X | | X | | | | |
| Goldstein[33] | | | | X | | | | |
| Sarli[34] | X | X | | X | X | | | X |
| Caplin[35] | X | X | | | | | | |
| Cianchi[36] | X | X | | X | X | | | |
| Gumus[37] | N/A | | | | | | | |
| Law[38] | X | | X | | | | | |
| Ratto[39] | X | | | X | X | | | |
| Wong[40] | N/A | | | | | | | |
| Yoshimatsu[41] | N/A | | | | | | | |

N/A: Unadjusted analyses only

*Surgeon and Hospital Factors*

Few studies adjust for hospital factors when assessing the association between lymph node evaluation and overall survival. Specifically, only one of the above studies explicitly mentions the potential confounding effect of these factors on survival. Bui et al. examine factors including teaching status, hospital volume, emergent surgeries.[4] However, several studies have demonstrated an association between additional hospital characteristics and survival including cooperative cancer group membership and hospital network characteristics. Further, no study accounted for variation in surgeon characteristics as a potential mediator between lymph node evaluation and survival.

*Receipt of Recommended Post-surgical care*

While the underlying mechanism for the relationship between lymph node evaluation and improved survival remains controversial, several groups have proposed that adequate lymph node evaluation may actually be an underlying marker of more comprehensive, higher-quality care.[16, 18, 22] Specifically, patients with more extensive lymph node evaluation may be more likely to receive guideline-recommended adjuvant therapy for their disease as well as more extensive follow-up and surveillance care. Current practice guidelines recommend that patients with AJCC stage III[42] (i.e. lymph-node positive disease) receive adjuvant chemotherapy and a series of post-surgical surveillance exams in the period following treatment in order to monitor disease progression and control. [13, 43-46] While previous research has identified an independent association between adequate lymph node evaluation,[13] adjuvant therapy,[42] comprehensive post-surgical care[13, 43-46] and lower mortality, no study has systematically evaluated how these combined interventions influence mortality.

***Factors Associated with Adequate Lymph Node Evaluation during Colon Cancer Resection***

*Patient Factors*

Current studies evaluating factors associated with adequate lymph node evaluation have specifically examined patient, surgeon and hospital factors that influence evaluation. However, they examine adequate evaluation as a benchmark and not a relative increase in performance. Specifically, patient factors including age, race, gender, insurance and extent of disease have all been demonstrated to influence removal of a higher number of lymph nodes (Table 3). Again, these studies do not account for additional unobserved confounders and fail to acknowledge that selection bias may be driving this relationship, particularly when certain individuals are likely to go to better quality surgeons or institutions.

**Table 3: Patient Factors Associated with Adequate Lymph Node Evaluation for Colon Cancer**

| **Study** | **Age** | **Gender** | **Race** | **Histology / Grade** | **Extent of disease** | **Co-morbidity** | **Insurance** |
|---|---|---|---|---|---|---|---|
| Baxter[19] | X | X | | X | X | | X |
| Bilimoria[28] | X | X | X | X | X | | |
| Nathan[21] | X | X | X | X | X | X | X |

*Surgeon Factors*

Surgeon factors that influence a higher lymph node evaluation are fairly limited in the literature. Specifically, only two studies have evaluated the impact of surgeon specialty and volume on the likelihood of adequate lymph node evaluation for colon cancer.[21, 28] Literature from the general surgical field indicates that several other factors may influence outcomes or quality measures including physician experience, board certification and years since medical

school. Specifically, physician age up to 50 years and more than 10 years of experience are associated with higher adoption rates of new procedures and techniques.[47] Further, physicians in solo practice in non-urban locations adopted the least number of new procedures annually, which was thought to be related to a lower amount of peer exposure to the use of new procedures or guidelines.

*Hospital Factors*

Several hospital characteristics have been significantly associated with adherence to guideline recommended lymph node evaluation. In a study of the National Quality Database, hospital type including NCI designated comprehensive cancer centers and academic institutions were significantly more likely to follow recommended evaluation guidelines.[28] Additionally, a study of elderly colon cancer patients identified the same hospital characteristics as predictive of higher lymph node evaluation.[21] However, no study has specifically evaluated how nodal evaluation prior to the implementation of guidelines was associated with performance after guidelines were published.

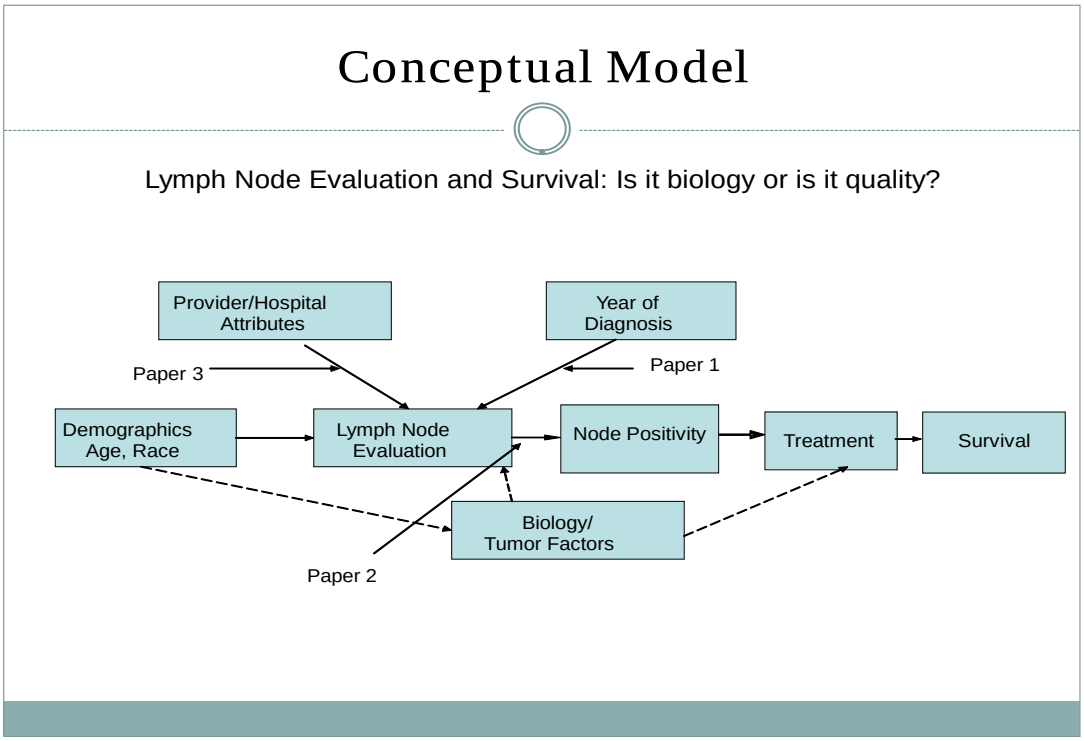
***Limitations to Current Research***

Current literature evaluating both predictors of lymph node evaluation and its ability to significantly influence survival are limited both in the extent to which potential confounders are addressed and their discussions regarding how improvement in quality guideline adherence might be achieved. This gap in knowledge presents an opportunity to further evaluate predictors of improvement in lymph node evaluation- not just the attainment of the quality measure. Further, current research is limited in the extent to which hospital factors drive the node evaluation-survival relationship. Studies fully incorporating these confounding factors may demonstrate that the survival relationship is more likely attributable primarily to hospital quality.

**Conceptual Model**

As seen in the literature review, three main groups of factors influence the adequacy of lymph node evaluation for colon cancer patients: patient, surgeon and hospital characteristics (Figure 1). Although the surgeon is ultimately responsible for the surgical treatment and extent of lymph node dissection, multiple patient characteristics can influence the treating surgeon. In addition to specific tumor characteristics, patient factors such as age, extent of comorbidities and the number of nodes present can all impact the number of nodes evaluated as well as survival.

**Figure 1: Conceptual Model of Factors that Influence Receipt of Adequate Lymph Node Evaluation and Receipt of Recommended Post-Surgical Care**




In addition to patient factors, surgeon factors significantly influence technique, knowledge and experience, which all differentially influence the likelihood of adequate lymph

node evaluation. Specifically, a surgeon's specialty, professional certification, years in practice and surgical volume all influence the ability to identify lymph nodes during surgical resection. Although a surgeon's decision to identify a larger number of lymph nodes should be independent of patient characteristics, tumor characteristics or unmeasured biological changes may influence a provider's ability to identify lymph nodes.

Lymph node evaluation can also be significantly influenced by hospital characteristics, which can influence the culture or expectations of surgical resection for individual surgeons. These factors include those characteristics that are known to influence other cancer quality outcomes such as survival. Such characteristics include hospital volume for colon procedures, type of ownership, teaching status and membership in a cancer cooperative group.

Receipt of adjuvant therapy, while also influenced by patient, provider and hospital characteristics, is modified by the receipt of adequate lymph node evaluation. In other words, individuals undergo adequate lymph node evaluation are more likely to receive quality care along the cancer continuum. Once they enter a high quality system, they continue to receive appropriate therapy in a timely manner.

**Contribution of the Dissertation to Previous Work**

Understanding the mechanism that influences the node-survival relationship and leads to improved adherence to guideline recommended care will be instrumental in the design of future quality improvement programs. While lymph node evaluation alone may not drive improved survival, understanding the best combined mechanisms for influencing guideline recommended care will be important for identifying those components that significantly improve the quality of colon cancer care in the US.

# Chapter 3: Association between Lymph Node Evaluation for Colon Cancer and Node Positivity over the Past 20 Years[48]

**Context:** Among patients surgically treated for colon cancer, better survival has been demonstrated in those with more lymph nodes evaluated. The presumed mechanism behind this association suggests that a more extensive lymph node evaluation reduces the risk of understaging, leading to improved survival.

**Objective:** To further evaluate the mechanism behind lymph node evaluation and survival, we examined the association between more extensive lymph node evaluation, identification of lymph node positive cancers and hazard of death.

**Design:** Observational cohort study

**Setting:** 1988-2008 Surveillance, Epidemiology and End Results (SEER) Program

**Patients:** 86,394 surgically treated colon cancer patients

**Main outcome measure:** We examined the relationship between lymph node evaluation and node positivity using Cochran-Armitage tests and multivariate logistic regression. The association between lymph node evaluation and hazard of death was evaluated using Cox Proportional Hazards modeling.

**Results:** The number of lymph nodes evaluated increased from 1988 to 2008, but did not result in a significant overall increase in lymph node positivity. During 1988-1990, 34.6% (n=3,875/11,200) of patients had ≥12 lymph nodes evaluated, increasing to 73.6% (n=9,798/13,310) during 2006-2008 ($p<0.001$); however, the proportion of node positive cancers

did not change with time (40% in 1988-1990 vs. 42% in 2006-2008 (p=0.53)). Although patients with high levels of lymph node evaluation were only slightly more likely to be node positive (adjusted odds ratio for 30-39 nodes vs. 1-8 nodes, 1.11; 95% Confidence Interval (CI), 1.02-1.20), these patients experienced significantly lower hazard of death compared with those with fewer nodes evaluated (adjusted hazard ratio for 30-39 nodes vs. 1-8 nodes, 0.66; 95% CI, 0.62-0.71).

**Conclusions:** The number of lymph nodes evaluated for colon cancer has markedly increased in the past two decades but was not associated with an overall shift toward higher staged cancers, questioning the upstaging mechanism as the primary basis for improved survival in patients with more lymph nodes evaluated.

**Background**

As wide-ranging quality improvement efforts emerge throughout the healthcare system,[23] finding mechanisms for optimizing cancer care through accurate staging and appropriate treatment has become an area of substantial interest to policy makers. Among patients surgically treated for colon cancer, several studies have demonstrated better survival for patients with more lymph nodes evaluated. Reported survival improvements among those with higher lymph node counts have approached 20% in some settings.[3, 6] The proposed mechanism behind this association suggests that a more extensive lymph node evaluation reduces the risk of understaging- in which inadequate assessment may incorrectly identify a patient with node-positive disease as node negative, thus failing to identify appropriate treatment. Based on these studies, most practice organizations and consensus panels now advocate for the surgical evaluation of 12 or more lymph nodes for acceptable staging of newly diagnosed colon cancer patients,[14, 26] although individual studies vary widely in their recommendations for the number of evaluated nodes necessary to accurately determine nodal status.[6, 22]

Recently, some studies have questioned the understaging mechanism, suggesting that efforts by payers and professional associations to increase the number of lymph nodes evaluated during colon cancer surgery may have a limited role in improving survival.[12, 15-16] On a hospital level, increasing the number of lymph nodes evaluated following colectomy for colon cancer has not been demonstrated to improve staging or survival in patients 65 year and older.[16] Other studies have suggested that while patients may experience improved staging when more lymph nodes are identified, the relationship between the number of nodes evaluated, staging, and survival is not simple, with higher lymph node evaluation not necessarily leading to finding higher staged cancers in select populations.[17] Combined, these results question the hypothesis that minimizing understaging is the underlying mechanism for the relationship between lymph

node evaluation and improved survival. We analyzed 20-year trends in the degree of lymph node evaluation for colon cancer and how they are associated with survival.

## Methods

### *Data*

We used the 1988-2008 Surveillance, Epidemiology, and End Results (SEER 9) cancer registry data. Sponsored by the National Cancer Institute, SEER collects and publishes cancer incidence, treatment and survival data from population-based cancer registries covering approximately 28% of the US population.[49-50] Specifically, SEER collects information on patient age, race/ethnicity, sex, year of diagnosis, tumor registry location, tumor depth, tumor grade, number of lymph nodes evaluated, number of positive lymph nodes and first course of treatment (not including chemotherapy). Overall and cancer-specific mortality are also reported, but not recurrence. A 98% case ascertainment is mandated, with annual quality-assurance studies.[49] This study was approved by the University of Minnesota Institutional Review Board.

### *Patients*

Included in our study were patients >18 years who were diagnosed with their first invasive adenocarcinoma of the colon from January 1, 1988, through December 31, 2008. We included only patients who underwent radical resection of their colon cancer as the first course of treatment according to SEER and would, therefore, be eligible for nodal evaluation.

Excluded from our study were patients whose cancer was diagnosed by autopsy or first cited on the death certificate; patients who underwent preoperative irradiation (as it may reduce the ability of surgeons to perform adequate nodal evaluation);[51] and patients with an unknown number of nodes examined.

*Assessment of Lymph Node Evaluation and Node Positivity*

Beginning in 1988, SEER has routinely recorded the number of nodes pathologically examined for each patient as well as the presence and number of positive lymph nodes (as a continuous measure). We categorized patients according to their level of lymph node evaluation in two ways, 1) receipt of ≥12 lymph nodes (yes/no), which is generally considered an acceptable level of lymph node evaluation for determining nodal status based on several clinical guidelines,[13-14, 26] and 2) a series of smaller lymph node categories (0, 1-8, 9-11, 12-15, 15-19, 20-29, 30-39, and ≥40) that allow for more extensive evaluation of the effect of lymph node evaluation on each outcome. We additionally categorized patients according to node positivity (yes/no), with at least one positive lymph node recorded as an indication of lymph node-positive disease.

*Statistical Analysis and Outcomes*

We evaluated differences in nodal evaluation, node positivity and patient characteristics across years of diagnosis, which were categorized into seven groups: 1988-1990, 1991-1993, 1994-1996, 1997-1999, 2000-2002, 2003-2005 and 2006-2008. First, we tested for trends in the proportion of patients with ≥12 lymph nodes evaluated and those with node-positive disease over time using the Cochran-Armitage test. Additionally, we evaluated differences in lymph node evaluation (using the smaller categories) and patient characteristics across time using the chi-square test.

After assessing this unadjusted relationship, we used logistic regression to examine the association between lymph node evaluation, patient demographics, tumor characteristics and relative odds of node positivity among those with at least one lymph node evaluated (yes/no). Finally, we evaluated the association between lymph node evaluation and 5-year hazard of death using Kaplan-Meier methods and Cox Proportional Hazards modeling. Kaplan-Meier methods were used to estimate unadjusted 5-year cumulative mortality across patient factors. Then, using patients as the unit of analysis, logistic regression and Cox models were adjusted for the level of

lymph node evaluation, age group (>50, 50-59, 60-69, 70-79, ≥80 years), race (White, Black, Other), sex, tumor extent (AJCC stage or T-stage), grade, tumor location, type of surgical resection according to SEER, receipt of post-operative radiation (yes/no), year of diagnosis, and registry.

There are additional factors that may explain survival that we could not include in our models. For example, we believe chemotherapy is part of the causal pathway between higher rates of lymph node evaluation and improved survival for patients with lymph node positive disease. That is, chemotherapy does not cause more lymph nodes to be evaluated, but those with higher lymph node evaluation may be more likely to receive chemotherapy when indicated (e.g. AJCC stage III disease), leading to improved survival.[16] However, SEER does not release receipt of adjuvant chemotherapy to researchers. As a result, differences in 5-year hazards of death will necessarily reflect the composite effect of lymph node evaluation in addition to other quality indicators such as chemotherapy. To take this potential factor into account, we stratified our results by nodal status at diagnosis to examine the relationship between nodal evaluation and survival among those with either node positive (AJCC stage III and IV) or node negative (AJCC stage I and II) disease.

In all models, we performed several sensitivity analyses (e.g. interaction analyses [Appendix 1], stratified analyses [Appendices 2 and 3] alternative category groupings [Appendix 4], removal of non-significant factors [Appendices 5 and 6]) to ensure that the observed effects were not an artifact of our modeling decisions. Because the effect of lymph node evaluation on odds of node-positivity may vary by tumor extent (e.g. T-stage) and patient characteristics (e.g. age at diagnosis), we tested for interactions between lymph node evaluation and these factors in all multivariate models. Further, because AJCC staging classifications are dependent on nodal status to determine stage and have changed over time,[52] we focused on T-stage as our proxy for tumor extent when evaluating factors associated with node positivity; however, both were

considered independently in the survival models [Appendix 7]. T-stage is defined as the depth of bowel penetration of the tumor in the colon, with more extensive bowel penetration indicative of more advanced T-stage.[53] Lymph nodes are not taken into account when assigning T-stage. Under all assumptions, conclusions remained unchanged. See Appendices 1- 7 for complete description of sensitivity analysis results.

We used SAS version 9.1(SAS Institute Inc., Cary, North Carolina) for all analyses. All comparisons were pre-planned. P-values were 2-sided with a level of significance of $\leq 0.05$.

**Results**

We identified 86,394 surgically-treated patients diagnosed with a primary invasive colon cancer from 1988 through 2008 in the SEER program after excluding patients with cancers diagnosed by autopsy or first cited on the death certificate (n=81); those who underwent preoperative irradiation (n=216) and those who had an unknown number of nodes evaluated (n=3,537). Over time, the distribution of patients shifted to those younger at diagnosis, with a higher proportion of proximal and T-stage 1 tumors (Table 4). Specifically, the proportion of patients diagnosed at <50 years of age increased from 6% (n=715) to 9% (n=1,234) between 1988-90 and 2006-08 (p<0.001). Over the same time period, the proportion of proximal tumors in the cohort increased from 55% (n=6,191) in 1988-1990 to 61% (n=8,231) in 2006-2008 periods (p=0.0001). Additionally, these patients were diagnosed at an earlier AJCC-stage, with only 16% (n=1,795) of tumors classified as AJCC stage I in 1988-1990 compared to 24.6% (n=3,270) in 2006-08 (p<0.001).

*Changes in Lymph Node Evaluation over Time*

Lymph node evaluation for colon cancer increased markedly from 1988 to 2008 (Table 4). During 1988-1990, only 34.6% (n=3,875) of patients were receiving acceptable (≥12) lymph node evaluation (Figure 2 and Table 4). By 1994-1996, 37.9% (n=4,362) of patients had ≥12

lymph nodes evaluated, with 46.8% (n=6,175) receiving this level of evaluation in 2000-2002 and 73.6% (n=9,798) in 2006-2008 ($p<0.001$).

*Proportion of Node Positive Cancers over Time*

Although the number of lymph nodes evaluated increased significantly over time, this change did not result in an increase in node positive cancers over the period 1988 to 2008 ($p=0.53$) (Figure 3). However, between T-stages, there were statistically significant but clinically modest increases in the proportion of node positive cancers as rates of lymph node evaluation increased. While patients with T-stage 2 tumors had relatively consistent rates of node positivity over time (16.8% in 1988-1990 to 19.1% in 2006-2008), those with T-stage 3 tumors had statistically significant increases in node positivity (38.8% in 1988-1990 to 49.8% in 2006-2008, $p<0.001$) in addition to T-1 and T-4 tumors (Figure 3).

*Association between Lymph Node Evaluation and Node Positivity*

In our study, 96.9% (n=83,671) of surgically-treated colon cancer patients had at least one lymph node evaluated (Table 5). Among these individuals, multivariate analyses demonstrated that, after adjusting for patient, tumor, and initial treatment factors, those with adequate lymph node evaluation (Model 1) were significantly more likely to have node-positive disease (adjusted odds ratio (OR) ≥12 vs. <12 nodes, 1.13; 95% Confidence Interval (CI), 1.09-1.17). However, those with very high levels of lymph node evaluation (Model 2) were only slightly more likely to be node positive compared to those with few nodes evaluated (adjusted OR for 30-39 nodes vs. 1-8 nodes, 1.11; 95% CI, 1.02-1.20). In addition to lymph node evaluation, younger age, higher T-stage and tumor grade were all associated with higher odds of node positivity. Interestingly, patients diagnosed in later years were also more likely to have node-positive disease (adjusted OR 2006-2008 vs. 1988-1990, 1.23; 95% CI, 1.16-1.30), after adjusting for level of lymph node evaluation.

*Association between Lymph Node Evaluation and Mortality*

Overall 5-year cumulative mortality was 46.9% (n=36,435) in our study for all surgically treated patients diagnosed with AJCC stage I-IV colon cancer. Although patients with higher levels of lymph node evaluation were only slightly more likely to have node-positive disease, these patients experienced significantly lower relative hazard of 5-year death compared to those with fewer nodes evaluated (adjusted hazard ratio (HR) for 30-39 nodes vs. 1-8 nodes, 0.66; 95% CI, 0.62-0.71) (Table 6a). When stratified by node positivity, patients with node positive disease (AJCC stages III and IV, adjusted HR for 30-39 nodes vs. 1-8 nodes 0.73; 95% CI 0.67-0.79) as well as node negative disease (AJCC stages I and II, adjusted HR for 30-39 nodes vs. 1-8 nodes 0.54; 95% CI 0.48-0.62) continued to experience lower relative hazard of death when more lymph nodes were evaluated (Table 6b). In addition to higher lymph node evaluation, distal cancer site and a later year of diagnosis were also associated with lower relative hazard of death. Older age at diagnosis, black race, more advance AJCC stage, and high tumor grade were all associated with higher 5-year relative hazard of death ($p<0.05$ for all).

**Discussion**

In this population-based study of patients surgically treated for colon cancer from 1988 through 2008, we found marked increases in lymph node evaluation over the past two decades. However, this improvement in lymph node evaluation has not been associated with an increase in the overall proportion of cancers that are node positive in the population. While patients with high levels of lymph node evaluation were only slightly more likely to be node positive than those with few nodes evaluated, patients with both node positive as well as node negative disease had significant reductions in mortality hazard attributable to high node counts. The combination of no substantive change in the proportion of patients with positive nodes concurrent to a large secular increase in the number of lymph nodes examined and the paradoxically better survival in patients with node negative compared to node positive disease who have greater numbers of nodes

examined suggests that upstaging cannot be the mechanism underlying the relationship between increased lymph node evaluation and colon cancer survival.

Initially, the primary mechanism for the observed association between more extensive lymph node evaluation and improved survival was believed to be upstaging. In other words, a more extensive evaluation of lymph nodes would result in more accurate identification of lymph node positive cancers. However, in a hospital-level analysis of surgically treated colon cancer patients aged 65 years and older, Wong et al. found no evidence of better 5-year survival among hospitals with higher levels of lymph node evaluation.[16] Further, they found that regardless of the number of lymph nodes a hospital evaluated, they were equally likely to find node positive tumors. In another study of surgically treated colon cancer patients with T3 disease, Baxter et al.[17] found that the odds of finding node positive cancers increased in patients with more lymph nodes evaluated- but only to a point. While the proportion of their patients found to with node positive disease increased with larger nodal counts at low levels (1-6 nodes), those with 7 nodes evaluated were as likely as patients with >30 nodes evaluated to be node positive- suggesting that other unmeasured factors may lead to identification of node positive disease, potentially influencing survival. Bui et al. further examined this relationship, noting that among patients with node-negative disease from the Ontario Cancer registry, higher lymph node counts were associated with improved survival; however patients with node-positive disease were not simultaneously evaluated.[4]

Our study builds on these previous studies conducted in select groups, presenting a population-based analysis of the relationship between lymph node evaluation, upstaging, and survival that is representative of adult colon cancer patients in the US and not limited to the elderly individuals or specific AJCC stages. After adjusting for patient, tumor and primary treatment factors, we found patients with node-negative disease had lower 5-year mortality when more lymph nodes were evaluated. This effect was unexpectedly larger than that observed for

patients with node positive disease. These findings suggest that providers who evaluate more lymph nodes may provide some other unmeasured care, leading to better outcomes. Alternatively, the relationship between nodes evaluated and survival may reflect an underlying interaction between the tumor and individual, influencing survival.[16, 22] In other words, tumor factors may stimulate lymph nodes to enlarge, reflecting immune system recognition of the tumor and more favorable survival outcomes. Although our results cannot provide insight into which mechanism underlies the observed patterns, our findings do indicate that more extensive lymph node evaluation unlikely leads to improved survival primarily through the more accurate detection of node-positive disease. These findings suggest that other factors besides upstaging, such as improved surgical quality or post-surgical care, may be the driving mechanism behind the lymph node-survival relationship. As a result, implementing wide-range quality-improvement initiatives to increase lymph node evaluation for colon cancer may have a limited effect on improving survival in this population.

Our results also confirm prior studies that indicate younger age,[17] more advanced tumor depth[54-55] and high tumor grade[17] are all important predictors of node-positivity in the population. Further, we identify year of diagnosis as an additional predictor of node-positivity, which may result from the adoption of new pathology or surgery techniques for harvesting lymph nodes or identifying micrometastases.[56-58] However, it is interesting to note that while the relative odds of identifying node-positive disease increased over time, the overall proportion of node-positive cancers did not significantly increase in the population despite large increases in the number of lymph nodes evaluated.

Finally, our results identify the continued inadequacy of lymph node evaluation, regardless of the role it may play in cancer staging or survival of patients. In a 2008 study of hospitals in the National Cancer Database, Bilimoria et al.[28] found that over 45% of hospitals were still performing below guideline recommendations for adequate lymph node evaluation (≥12

nodes), more than 12 years after the first guideline was published. They suggested that although the proportion of hospitals consistently performing guideline recommended staging increased markedly from 1996-1997 to 2004-2005, the large number of US hospitals remaining non-adherent with lymph node evaluation guidelines in 2004-2005 may indicate to some that this quality measure is not appropriate or less relevant for some cases. Our study builds on these findings and identifies that more than 25% of patients still had fewer than 12 lymph nodes evaluated in 2006-2008.

Although our study does provide further insight into the relationship between lymph node evaluation and survival in a population-based setting, we acknowledge several data-related limitations. First, SEER does not collect information on co-morbidities that may have affected the ability of the surgeon to remove an adequate tissue sample for lymph node evaluation. However, patients undergoing resection should have had an underlying level of general health to undergo the procedure. Additionally, we cannot differentiate between patients diagnosed through screening versus symptomatic presentation. However, others have shown that the proportion of patients diagnosed through screening has increased over time and is consistent with the shift toward earlier stages at diagnosis over time in our study.[59-60] Finally, we are unable to determine the reason behind the extensiveness of lymph node evaluation for an individual cancer. Importantly, these results are more representative of cancers diagnosed in the US population because the data are not limited to elderly individuals and include all patients diagnosed with AJCC stage I-IV disease.

In conclusion, the number of lymph nodes evaluated for colon cancer markedly increased in the past two decades but was not associated with an overall shift toward higher staged cancers, questioning the upstaging mechanism as the primary basis for improved survival in patients with more lymph nodes evaluated.

**Table 4: Assessment of Changes in Lymph Node Evaluation, Rates of Node Positivity, and Patient Characteristics Over Time (N=86,394)**

| | 1988-1990 | 1991-1993 | 1994-1996 | 1997-1999 | 2000-2002 | 2003-2005 | 2006-2008 | P-Value[a] |
|---|---|---|---|---|---|---|---|---|
| **Number of Patients** | 11,200 | 11,517 | 11,492 | 12,545 | 13,209 | 13,121 | 13,310 | |
| **Lymph Node Evaluation over Time** | | | | | | | | |
| **≥12 Lymph Nodes Evaluated (%)** | 34.6 | 36.4 | 37.9 | 41.9 | 46.8 | 55.4 | 73.6 | <0.001[b] |
| **Lymph Nodes Evaluated (%)** | | | | | | | | <0.001 |
| **0** | 5.6 | 4.4 | 4.0 | 2.8 | 2.6 | 1.9 | 1.4 | |
| **1-8** | 44.3 | 44.0 | 42.1 | 38.7 | 33.9 | 27.0 | 13.1 | |
| **9-11** | 15.5 | 15.2 | 15.9 | 16.6 | 16.7 | 15.6 | 11.9 | |
| **12-15** | 14.5 | 15.2 | 15.5 | 16.8 | 16.9 | 18.6 | 21.0 | |
| **16-19** | 8.3 | 8.9 | 9.3 | 10.0 | 11.0 | 13.3 | 18.3 | |
| **20-29** | 8.5 | 9.2 | 9.8 | 10.6 | 13.1 | 15.8 | 23.3 | |
| **30-39** | 2.2 | 2.2 | 2.3 | 2.9 | 3.8 | 4.6 | 6.9 | |
| **≥40** | 1.0 | 1.0 | 1.1 | 1.6 | 2.0 | 3.1 | 4.1 | |
| **Proportion of Node Positive Cancers over Time** | | | | | | | | |
| **Node Positive Cancers (%)** | 40.3 | 39.8 | 41.2 | 41.4 | 41.5 | 41.4 | 42.4 | 0.53[b] |

[a] P-value indicates significance of the Chi-square test unless otherwise noted.
[b] Cochran-Armitage test for trend
NOS: not otherwise specified

**Table 4 (Continued): Assessment of Changes in Lymph Node Evaluation, Rates of Node Positivity, and Patient Characteristics Over Time (N=86,394)**

| | 1988-1990 | 1991-1993 | 1994-1996 | 1997-1999 | 2000-2002 | 2003-2005 | 2006-2008 | P-Value[a] |
|---|---|---|---|---|---|---|---|---|
| **Patient Demographics, %** | | | | | | | | |
| **Age at Diagnosis** | | | | | | | | |
| **<50** | 6.4 | 7.4 | 7.4 | 8.4 | 8.5 | 9.2 | 9.3 | <0.001 |
| **50-59** | 11.6 | 11.6 | 12.8 | 13.5 | 14.8 | 17.4 | 18.3 | |
| **60-69** | 26.1 | 24.4 | 23.6 | 22.2 | 22.2 | 21.9 | 23.7 | |
| **70-79** | 32.3 | 32.7 | 31.9 | 31.5 | 30.2 | 27.6 | 25.6 | |
| **≥80** | 23.6 | 23.9 | 24.3 | 24.4 | 24.3 | 23.9 | 23.1 | |
| **Race** | | | | | | | | |
| **White** | 85.7 | 83.9 | 83.1 | 82.0 | 79.9 | 78.8 | 78.4 | <0.001 |
| **Black** | 8.4 | 9.3 | 9.1 | 9.5 | 10.2 | 10.9 | 11.3 | |
| **Other** | 15.9 | 6.8 | 7.8 | 8.5 | 9.9 | 10.3 | 10.4 | |
| **Sex** | | | | | | | | |
| **Male** | 47.5 | 46.3 | 46.0 | 47.0 | 47.1 | 47.3 | 47.3 | 0.19 |
| **Female** | 52.5 | 53.7 | 54.0 | 53.0 | 52.9 | 52.7 | 52.7 | |

[a] P-value indicates significance of the Chi-square test unless otherwise noted.
[b] Cochran-Armitage test for trend
NOS: not otherwise specified

**Table 4 (Continued): Assessment of Changes in Lymph Node Evaluation, Rates of Node Positivity, and Patient Characteristics Over Time (N=86,394)**

| | 1988-1990 | 1991-1993 | 1994-1996 | 1997-1999 | 2000-2002 | 2003-2005 | 2006-2008 | P-Value[a] |
|---|---|---|---|---|---|---|---|---|
| **Tumor Characteristics, %** | | | | | | | | |
| **AJCC Stage** | | | | | | | | |
| **1** | 16.0 | 17.6 | 17.9 | 19.8 | 22.0 | 23.7 | 24.6 | <0.001 |
| **2** | 37.4 | 36.9 | 35.9 | 34.5 | 32.8 | 31.4 | 31.2 | |
| **3** | 27.7 | 28.0 | 29.3 | 29.1 | 29.8 | 29.7 | 29.6 | |
| **4** | 18.9 | 17.5 | 16.9 | 16.6 | 15.4 | 15.2 | 14.6 | |
| **T-stage** | | | | | | | | |
| **1** | 8.7 | 9.2 | 8.8 | 10.2 | 12.2 | 14.0 | 14.7 | <0.001 |
| **2** | 9.5 | 10.9 | 11.7 | 12.6 | 13.4 | 13.9 | 14.5 | |
| **3** | 49.9 | 49.6 | 50.6 | 50.5 | 49.6 | 54.8 | 57.8 | |
| **4** | 31.9 | 30.3 | 28.8 | 26.7 | 24.8 | 17.3 | 13.0 | |
| **Tumor Grade** | | | | | | | | |
| **1/2** | 73.1 | 75.3 | 75.5 | 76.2 | 76.1 | 75.7 | 76.7 | <0.001 |
| **3/4** | 17.4 | 19.4 | 20.5 | 20.7 | 20.7 | 21.0 | 20.0 | |
| **Unknown** | 9.5 | 5.3 | 4.0 | 3.1 | 3.2 | 3.4 | 3.3 | |
| **Tumor Location** | | | | | | | | |
| **Proximal** | 55.3 | 56.8 | 58.2 | 59.3 | 60.5 | 60.5 | 61.8 | <0.001 |
| **Distal** | 43.6 | 41.8 | 40.4 | 39.3 | 38.0 | 38.0 | 36.8 | |
| **Other** | 1.2 | 1.4 | 1.4 | 1.3 | 1.5 | 1.5 | 1.4 | |

[a] P-value indicates significance of the Chi-square test unless otherwise noted.
[b] Cochran-Armitage test for trend
NOS: not otherwise specified

**Table 4 (Continued): Assessment of Changes in Lymph Node Evaluation, Rates of Node Positivity, and Patient Characteristics Over Time (N=86,394)**

| | 1988-1990 | 1991-1993 | 1994-1996 | 1997-1999 | 2000-2002 | 2003-2005 | 2006-2008 | P-Value[a] |
|---|---|---|---|---|---|---|---|---|
| **Initial Treatment, %** | | | | | | | | |
| **SEER Type of Surgical Resection** | | | | | | | | <0.01 |
| **Partial Colectomy** | 44.5 | 41.6 | 40.4 | 43.5 | 39.8 | 42.2 | 42.5 | |
| **Subtotal Colectomy/ Hemicolectomy** | 46.2 | 50.1 | 51.2 | 50.6 | 55.7 | 55.3 | 55.1 | |
| **Total Colectomy** | 1.1 | 1.0 | 1.2 | 1.0 | 1.1 | 1.2 | 1.3 | |
| **Total Proctocolectomy** | 0.6 | 0.5 | 0.6 | 0.3 | 0.2 | 0.2 | 0.3 | |
| **Colectomy/ Coloproctectomy with en bloc resection of other organs** | 7.2 | 6.6 | 6.3 | 4.3 | 2.8 | 0.7 | 0.4 | |
| **Colectomy, NOS*** | 0.4 | 0.2 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | |
| **Post-operative Radiation** | | | | | | | | <0.01 |
| **No** | 96.7 | 97.3 | 97.1 | 97.6 | 97.8 | 98.1 | 98.7 | |
| **Yes** | 3.3 | 2.7 | 2.9 | 2.4 | 2.2 | 1.9 | 1.3 | |

[a] P-value indicates significance of the Chi-square test unless otherwise noted.
[b] Cochran-Armitage test for trend
NOS: not otherwise specified

**Table 5: Relative Odds of Node Positivity among those with at Least One Lymph Node Evaluated, Multivariate Logistic Regression (N=83,671)**

| | Odds Ratios [95% Confidence Interval] | |
|---|---|---|
| | Model 1<br>N=83,671 | Model 2<br>N=83,671 |
| **≥12 Lymph Nodes Evaluated** | | |
| **No** | Ref | |
| **Yes** | **1.13 [1.09, 1.17]** | |
| **Lymph Nodes Evaluated** | | |
| **1-8** | | Ref |
| **9-11** | | **1.28 [1.23, 1.34]** |
| **12-15** | | **1.29 [1.24, 1.35]** |
| **16-19** | | **1.28 [1.21, 1.34]** |
| **20-29** | | **1.19 [1.13, 1.24]** |
| **30-39** | | **1.11 [1.02, 1.20]** |
| **≥40** | | 1.06 [0.96, 1.18] |
| **Age at Diagnosis** | | |
| **<50** | Ref | Ref |
| **50-59** | **0.89 [0.84, 0.96]** | **0.89 [0.84, 0.95]** |
| **60-69** | **0.78 [0.73, 0.83]** | **0.77 [0.73, 0.82]** |
| **70-79** | **0.64 [0.60, 0.68]** | **0.63 [0.60, 0.67]** |
| **≥80** | **0.52 [0.49, 0.56]** | **0.52 [0.49, 0.55]** |
| **Race** | | |
| **White** | Ref | Ref |
| **Black** | **1.18 [1.12, 1.24]** | **1.17 [1.11, 1.24]** |
| **Other** | **1.19 [1.11, 1.27]** | **1.19 [1.11, 1.27]** |
| **Sex** | | |
| **Male** | Ref | Ref |
| **Female** | 0.97 [0.94, 1.00] | 0.97 [0.94, 1.00] |
| **T-stage** | | |
| **1** | Ref | Ref |
| **2** | **2.49 [2.27, 2.72]** | **2.46 [2.25, 2.69]** |
| **3** | **7.98 [7.38, 8.63]** | **7.88 [7.29, 8.52]** |
| **4** | **20.34 [18.74, 22.09]** | **20.15 [18.56, 21.88]** |
| **Tumor Grade** | | |
| **1/2** | Ref | Ref |
| **3/4** | **2.06 [1.98, 2.14]** | **2.06 [1.98, 2.14]** |
| Unknown | 0.99 [0.91, 1.08] | 0.99 [0.91, 1.08] |
| **Tumor Location** | | |
| **Proximal** | Ref | Ref |
| **Distal** | **1.09 [1.05, 1.13]** | **1.09 [1.05, 1.14]** |
| **Other** | 1.12 [0.99, 1.28] | 1.13 [0.99, 1.29] |

| Table 5 (Continued): Relative Odds of Node Positivity among those with at Least One Lymph Node Evaluated, Multivariate Logistic Regression (N=83,671) | | |
|---|---|---|
| | **Odds Ratios [95% Confidence Interval]** | |
| | Model 1 N=83,671 | Model 2 N=83,671 |
| **Type of Surgical Resection** | | |
| **Partial Colectomy** | Ref | Ref |
| **Subtotal Colectomy/ Hemicolectomy** | 0.98 [0.95, 1.02] | 0.98 [0.94, 1.01] |
| **Total Colectomy** | **0.78 [0.67, 0.90]** | **0.79 [0.68, 0.92]** |
| **Total Proctocolectomy** | 1.08 [0.84, 1.39] | 1.10 [0.85, 1.41] |
| **Colectomy/Coloproctectomy with en bloc resection of other organs** | **0.86 [0.78, 0.93]** | **0.85 [0.79, 0.93]** |
| **Colectomy, NOS** | **0.85 [0.62, 1.17]** | **0.85 [0.62, 1.17]** |
| **Year of Diagnosis** | | |
| **1988-1990** | Ref | Ref |
| **1991-1993** | 0.97 [0.92, 1.03] | 0.97 [0.92, 1.03] |
| **1994-1996** | 1.04 [0.98, 1.10] | 1.04 [0.98, 1.10] |
| **1997-1999** | **1.06 [1.00, 1.12]** | **1.06 [1.00, 1.12]** |
| **2000-2002** | **1.11 [1.05, 1.17]** | **1.10 [1.04, 1.17]** |
| **2003-2005** | **1.19 [1.12, 1.26]** | **1.18 [1.12, 1.25]** |
| **2006-2008** | **1.23 [1.16, 1.30]** | **1.22 [1.15, 1.2]** |
| **Registry** | | |
| **Iowa** | Ref | Ref |
| **San-Francisco-Oakland** | 1.00 [0.95, 1.06] | 1.00 [0.95, 1.06] |
| **Connecticut** | **1.06 [1.01, 1.12]** | **1.06 [1.00, 1.12]** |
| **Metropolitan Detroit** | **1.08 [1.02, 1.14]** | **1.08 [1.02, 1.14]** |
| **Hawaii** | **1.17 [1.07, 1.28]** | **1.17 [1.07, 1.28]** |
| **New Mexico** | **1.12 [1.04, 1.21]** | **1.12 [1.04, 1.21]** |
| **Seattle (Puget Sound)** | 1.04 [0.98, 1.10] | 1.04 [0.98, 1.10] |
| **Utah** | 1.08 [0.99, 1.17] | 1.09 [0.99, 1.18] |
| **Atlanta** | **1.16 [1.08, 1.24]** | **1.15 [1.08, 1.24]** |
| **C-Index** | **0.74** | **0.74** |

Bold indicates $p<0.05$

**Table 6a: Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models[+]**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death All Patients N=86,394 | **Unadjusted 5-Year Cumulative Mortality (%)* N=86,394** |
|---|---|---|
| **Lymph Nodes Evaluated** | | |
| **0** | **1.23 [1.17, 1.30]** | 55.4 |
| **1-8** | Ref | 50.5 |
| **9-11** | **0.87 [0.85, 0.90]** | 48.7 |
| **12-15** | **0.83 [0.80, 0.85]** | 46.6 |
| **16-19** | **0.74 [0.71, 0.77]** | 42.9 |
| **20-29** | **0.73 [0.70, 0.76]** | 41.1 |
| **30-39** | **0.66 [0.62, 0.71]** | 35.3 |
| **≥40** | **0.64 [0.58, 0.70]** | 33.3 |
| **Age at Diagnosis** | | |
| **<50** | Ref | 34.7 |
| **50-59** | **1.11 1.06, 1.18]** | 35.4 |
| **60-69** | **1.37 [1.30, 1.43]** | 40.2 |
| **70-79** | **1.90 [1.81, 1.99]** | 47.3 |
| **≥80** | **3.30 [3.14, 3.46]** | 63.7 |
| **Race** | | |
| **White** | Ref | 47.1 |
| **Black** | **1.19 [1.15, 1.23]** | 52.1 |
| **Other** | 0.89 [0.85, 0.94] | 39.6 |
| **Sex** | | |
| **Male** | Ref | 48.2 |
| **Female** | **0.88 [0.86, 0.90]** | 45.8 |
| **AJCC Stage** | | |
| **1** | Ref | 22.0 |
| **2** | **1.68 [1.61, 1.75]** | 35.9 |
| **3** | **3.05 [2.93, 3.17]** | 51.6 |
| **4** | **11.86 [11.39, 12.35]** | 92.9 |
| **Tumor Grade** | | |
| **1/2** | Ref | 44.0 |
| **3/4** | **1.36 [1.33, 1.39]** | 59.6 |
| **Unknown** | 1.00 [0.95, 1.06] | 39 |

**Table 6a (Continued): Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models[+]**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death All Patients N=86,394 | **Unadjusted 5-Year Cumulative Mortality (%)* N=86,394** |
|---|---|---|
| **Tumor Location** | | |
| **Proximal** | Ref | 48.9 |
| **Distal** | **0.85 [0.82, 0.87]** | 43.5 |
| **Other** | **1.17 [1.08, 1.26]** | 59.1 |
| **Type of Surgical Resection** | | |
| **Partial Colectomy** | Ref | 44.3 |
| **Subtotal Colectomy/ Hemicolectomy** | 0.99 [0.97, 1.03] | 47.6 |
| **Total Colectomy** | **1.29 [1.17, 1.42}** | 49.5 |
| **Total Proctocolectomy** | 1.04 [0.89, 1.23] | 52.6 |
| **Colectomy/Coloproctectomy with en bloc resection of other organs** | 1.01 [0.96, 1.06] | 61.9 |
| **Colectomy, NOS** | **1.30 [1.11, 1.51]** | 68.6 |
| **Post-operative Radiation** | | |
| **No** | Ref | 46.6 |
| **Yes** | **1.21 [1.14, 1.28]** | 59.8 |
| **Year of Diagnosis** | | |
| **1988-1990** | Ref | 53.1 |
| **1991-1993** | **0.93 [0.90, 0.96]** | 50.6 |
| **1994-1996** | **0.95 [0.91, 0.98]** | 50.2 |
| **1997-1999** | **0.90 [0.87, 0.90]** | 48.0 |
| **2000-2002** | **0.83 [0.80, 0.86]** | 44.1 |
| **2003-2005** | **0.74 [0.72, 0.77]** | - |
| **2006-2008** | **0.73 [0.69, 0.77]** | - |
| **Registry** | | |
| **Iowa** | Ref | 47.2 |
| **San-Francisco-Oakland** | 1.03 [0.99, 1.07] | 47.3 |
| **Connecticut** | **1.05 [1.01, 1.09]** | 48.3 |
| **Metropolitan Detroit** | **1.09 [1.05, 1.13]** | 49.6 |
| **Hawaii** | 1.05 [0.98, 1.12] | 40.6 |
| **New Mexico** | **1.08 [1.03, 1.14]** | 46.4 |
| **Seattle (Puget Sound)** | 0.97 [0.93, 1.01] | 44.5 |
| **Utah** | **1.09 [1.03, 1.15]** | 46.1 |
| **Atlanta** | **1.06 [1.02, 1.11]** | 46.7 |

Bold indicates $p<0.05$ + Cox Proportional Hazards Models adjusted for all other factors listed. *Estimates from unadjusted Kaplan-Meier Survival curves. Note: As these are unadjusted mortality estimates across risk factors, the relative hazard ratios cannot be directly calculated by ratios of these values.

**Table 6b: Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models by Node-Positivity Status[+]**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Negative Patients (AJCC Stage I and II) N=47,162 | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Positive Patients (AJCC Stage III and IV) N=39,232 |
|---|---|---|
| **Lymph Nodes Evaluated** | | |
| **0** | **1.22 [1.11, 1.33]** | **1.23 [1.15, 1.33]** |
| **1-8** | Ref | Ref |
| **9-11** | **0.83 [0.79, 0.88]** | **0.89 [0.86, 0.93]** |
| **12-15** | **0.79 [0.75, 0.83]** | **0.85 [0.82, 0.88]** |
| **16-19** | **0.69 [0.65, 0.74]** | **0.77 [0.74, 0.81]** |
| **20-29** | **0.65 [0.61, 0.69]** | **0.77 [0.74, 0.81]** |
| **30-39** | **0.54 [0.48, 0.62]** | **0.73 [0.67, 0.79]** |
| **≥40** | **0.53 [0.44, 0.63]** | **0.70 [0.63, 0.78]** |
| **Age at Diagnosis** | | |
| **<50** | Ref | Ref |
| **50-59** | **1.48 [1.28, 1.71]** | **1.09 [1.03, 1.16]** |
| **60-69** | **2.14 [1.88, 2.45]** | **1.29 [1.23, 1.36]** |
| **70-79** | **3.77 [3.31, 4.29]** | **1.65 [1.57, 1.74]** |
| **≥80** | **7.80 [6.85, 8.87]** | **2.52 [2.38, 2.65]** |
| **Race** | | |
| **White** | Ref | Ref |
| **Black** | **1.36 [1.28, 1.45]** | **1.13 [1.08, 1.18]** |
| **Other** | 0.86 [0.79, 0.95] | 0.91 [0.85, 0.96] |
| **Sex** | | |
| **Male** | Ref | Ref |
| **Female** | **0.76 [0.73, 0.78]** | **0.95 [0.92, 0.97]** |
| **AJCC Stage** | | |
| **1** | Ref | - |
| **2** | **1.68 [1.62, 1.75]** | **-** |
| **3** | **-** | Ref |
| **4** | **-** | **3.96 [3.85, 4.07]** |

**Table 6b (Continued): Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models by Node-Positivity Status[+]**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Negative Patients (AJCC Stage I and II) N=47,162 | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Positive Patients (AJCC Stage III and IV) N=39,232 |
|---|---|---|
| **Tumor Grade** | | |
| **1/2** | Ref | Ref |
| **3/4** | **1.15 [1.10, 1.21]** | **1.46 [1.42, 1.50]** |
| **Unknown** | 0.92 [0.85, 1.00] | 1.09 [1.01, 1.17] |
| **Tumor Location** | | |
| **Proximal** | Ref | Ref |
| **Distal** | 0.96 [0.92, 1.01] | **0.78 [0.76, 0.86]** |
| **Other** | **1.22 [1.05, 1.42]** | **1.16 [1.05, 1.26]** |
| **Type of Surgical Resection** | | |
| **Partial Colectomy** | Ref | Ref |
| **Subtotal Colectomy/ Hemicolectomy** | 1.02 [0.98, 1.07] | 0.99 [0.95, 1.02] |
| **Total Colectomy** | **1.50 [1.29, 1.75}** | **1.21 [1.06, 1.37}** |
| **Total Proctocolectomy** | 1.17 [0.87, 1.59] | 1.00 [0.83, 1.22] |
| **Colectomy/Coloproctectomy with en bloc resection of other organs** | **1.29 [1.17, 1.41]** | 0.91 [0.86, 0.96] |
| **Colectomy, NOS** | **1.20 [0.78, 1.87]** | **1.32 [1.13, 1.57]** |
| **Post-operative Radiation** | | |
| **No** | Ref | Ref |
| **Yes** | **1.63 [1.45, 1.85]** | **1.10 [1.03, 1.18]** |

Bold indicates $p<0.05$

+ Cox Proportional Hazards Models adjusted for all other factors listed.

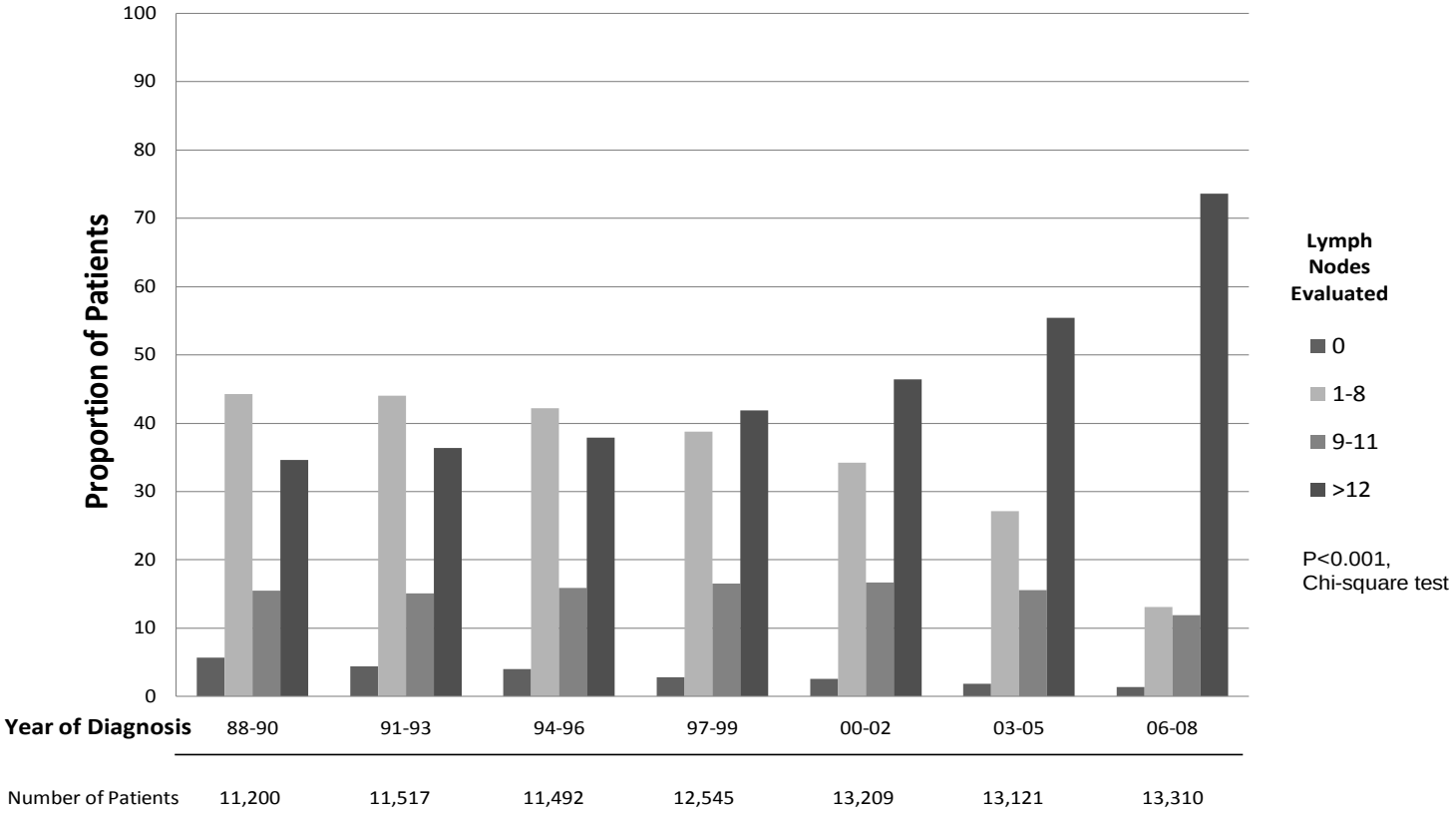
**Table 6b (Continued): Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models by Node-Positivity Status[+]**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Negative Patients (AJCC Stage I and II) N=47,162 | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Positive Patients (AJCC Stage III and IV) N=39,232 |
|---|---|---|
| **Year of Diagnosis** | | |
| **1988-1990** | Ref | Ref |
| **1991-1993** | 0.98 [0.93, 1.05] | **0.90 [0.86, 0.94]** |
| **1994-1996** | 0.96 [0.91, 1.02] | **0.94 [0.90, 0.98]** |
| **1997-1999** | 0.95 [0.89, 1.01] | **0.87 [0.84, 0.91]** |
| **2000-2002** | **0.89 [0.83, 0.94]** | **0.79 [0.76, 0.83]** |
| **2003-2005** | **0.85 [0.80, 0.91]** | **0.68 [0.65, 0.72]** |
| **2006-2008** | **0.88 [0.81, 0.96]** | **0.66 [0.62, 0.70]** |
| **Registry** | | |
| **Iowa** | Ref | Ref |
| **San-Francisco-Oakland** | 1.04 [0.98, 1.11] | 1.01 [0.97, 1.06] |
| **Connecticut** | **1.12 [1.06, 1.19]** | 1.00 [0.96, 1.05] |
| **Metropolitan Detroit** | **1.16 [1.09, 1.24]** | 1.05 [0.99, 1.10] |
| **Hawaii** | 1.00 [0.89, 1.13] | 1.06 [0.97, 1.14] |
| **New Mexico** | **1.12 [1.03, 1.23]** | 1.06 [0.99, 1.13] |
| **Seattle (Puget Sound)** | 0.98 [0.91, 1.04] | 0.96 [0.95, 1.02] |
| **Utah** | **1.10 [1.00, 1.21]** | **1.08 [1.00, 1.06]** |
| **Atlanta** | **1.18 [1.09, 1.28]** | 1.00 [0.95, 1.06] |

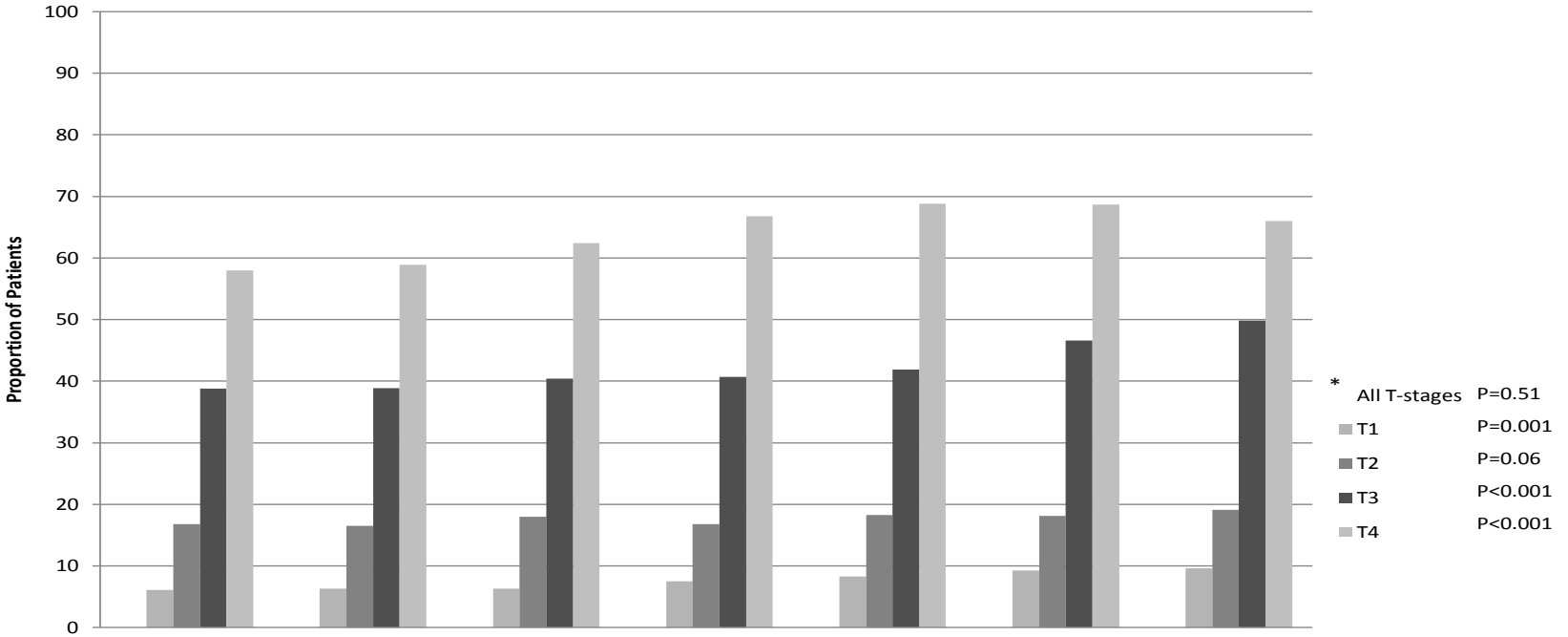
Bold indicates $p<0.05$

+ Cox Proportional Hazards Models adjusted for all other factors listed.

**Figure 2: Colon Cancer Lymph Node Evaluation Over Time (N=86, 394)**



## Figure 3: Colon Cancer Lymph Node Positivity Over Time, By T-Stage (N=86,394)




| Year of Diagnosis | 88-90 | 91-93 | 94-96 | 97-99 | 00-02 | 03-05 | 06-08 |
|---|---|---|---|---|---|---|---|
| Total Number of Patients | | | | | | | |
| Total | 11,200 | 11,517 | 11,492 | 12,545 | 13,209 | 13,121 | 13,310 |
| T1 | 972 | 1,055 | 1,022 | 1,279 | 1,611 | 1,830 | 1,958 |
| T2 | 1,069 | 1,265 | 1,339 | 1,576 | 1,773 | 1,827 | 1,926 |
| T3 | 5,583 | 5,713 | 5,819 | 6,331 | 6,552 | 7,190 | 7,698 |
| T4 | 3,576 | 3,484 | 3,312 | 3,359 | 3,273 | 2,274 | 1,728 |

* Cochran-Armitage test for trend evaluating changes in lymph node positive cancer over time, overall and by T-stage. 2-sided p-values

# Chapter 4: Quality of Care Along the Cancer Continuum: Does Receiving Adequate Lymph Node Evaluation for Colon Cancer Lead to More Comprehensive Post-Surgical Care?

*Background:* Among surgically treated patients with colon cancer, lower mortality has been demonstrated in those with ≥12 lymph nodes evaluated. We examined whether patients receiving adequate lymph node evaluation were also more likely to receive comprehensive post-surgical care, leading to lower mortality.

*Methods:* We used the 1992-2007 SEER-Medicare data to identify surgically-treated AJCC stage III colon cancer patients. We used chi-square analyses and logistic regression to evaluate the association between adequate (≥12) lymph node evaluation and receipt of post-surgical care (adjuvant chemotherapy, surveillance colonoscopy, computed tomography scans and carcinoembryonic testing) and Cox proportional hazards regression to evaluate 10-year overall mortality, adjusting for post-surgical care.

*Results:* Among 17,906 surgically treated stage III colon cancer patients, individuals with adequate lymph node evaluation were no more likely to receive comprehensive post-surgical care than those with <12 nodes evaluated ($p>0.05$ for all). Adequate lymph node evaluation was associated with lower overall mortality (HR: 0.88; 95% CI [0.83-0.88]), but among 3-year survivors, the impact of adequate lymph node evaluation on lower mortality was diminished (HR: 0.94; 95% CI [0.88-1.01]). However, receiving comprehensive post-surgical care was associated with continued lower mortality in 3-year survivors.

*Conclusions:* Adequate lymph node evaluation for colon cancer was associated with lower mortality at diagnosis. However, after patients survived 3 years, the association between lymph

node evaluation and lower hazard of death was no longer significant; however, post-surgical care remained strongly associated with lower long-term mortality, indicating that post-surgical care may partially explain the relationship between lymph node evaluation and mortality.

**Background**

With more than 100,000 new cases of colon cancer diagnosed in 2010,[23] identifying pathways for improved treatment and survival is critical for reducing the burden of this disease on the population.[2, 23] Several studies have demonstrated lower mortality among surgically treated colon cancer patients who have a more extensive lymph node evaluation. As a result, several practice organizations now advocate for the surgical evaluation of 12 or more lymph nodes for acceptable staging of newly diagnosed colon cancer patients.[11-14] One proposed mechanism to explain this association is that a more extensive lymph node evaluation reduces the risk of understaging, where a node-positive patient is incorrectly identified as node-negative. As a result, understaged patients may receive less aggressive adjuvant therapy or post-surgical care according to recommended guidelines.[15, 22] However, several studies are now questioning this mechanism, demonstrating that more extensive lymph node evaluation has not necessarily resulted in a shift towards higher staged colon cancers.[16-17] Rather, higher lymph node counts are associated with lower mortality regardless of whether patients are identified as having node-positive or node-negative disease.[18, 48]

While the underlying explanation for the node count-mortality relationship remains controversial, several groups have proposed that adequate lymph node evaluation may actually be a marker of more comprehensive, higher-quality care.[16, 18, 22] Specifically, patients with more extensive lymph node evaluation may be more likely to receive guideline-recommended adjuvant therapy for their disease as well as more extensive follow-up and surveillance care compared with patients who receive inadequate lymph node evaluation. Current practice guidelines recommend that patients with AJCC stage III[42] (i.e. lymph-node positive disease) receive adjuvant chemotherapy and a series of post-surgical surveillance exams in the period following treatment in order to monitor disease progression and control (Table 7).[13, 42-46] Previous research has identified independent associations between adequate lymph node evaluation,[6] adjuvant

therapy,[13, 43-44] comprehensive post-surgical care[13, 43-46] and lower mortality- however, no study has systematically evaluated how these combined interventions influence mortality. Our study further examines the relationship between adequate lymph node evaluation and mortality by evaluating whether adequate lymph node evaluation is associated with more comprehensive post-surgical care for colon cancer patients, partially explaining the association between more extensive lymph node evaluation and lower mortality.

**Methods**

*Data*

We used the 1992-2007 Surveillance, Epidemiology, and End Results (SEER) cancer registry data linked to Medicare enrollment records and utilization data (SEER-Medicare).[61] SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28% of the US population.[62] The SEER-Medicare Patient Entitlement and Diagnosis Summary File (PEDSF) includes patient characteristics, primary tumor site, tumor stage and grade, first course of treatment (including surgery and irradiation), follow-up for vital status (survival), and number of lymph nodes pathologically examined.[49]

Medicare provides comprehensive health care for approximately 97% of the U.S. population aged 65 or older.[61] Cancer cases reported to SEER have been matched to the Medicare master enrollment file in order to facilitate population-based health services research. Medicare eligibility has been identified for 93% of people 65 or older identified by SEER.[61] For Medicare enrollees who do not participate in a managed care plan, claims data are available through the Medicare Provider Analysis and Review (MedPAR) file, the National Claims History (NCH) file, and the Outpatient Standard Analytic File (SAF). Claims for hospitalizations and inpatient procedures are available in the MedPAR and NCH files, while office visits are captured through a

combination of NCH files for provider charges and Outpatient SAFs file for facility charges. This study was approved by the University of Minnesota Institutional Review Board.

*Patients*

We included 17,906 patients 66 years of age or older who were diagnosed with AJCC stage III adenocarcinoma of the colon from January 1, 1992, through December 31, 2007 and underwent radical resection for colon cancer (partial colectomy, hemicolectomy, total colectomy, total proctocolectomy, or coloproctotectomy) as the first course of treatment according to SEER and Medicare (Appendix 8). We excluded patients whose cancer was diagnosed by autopsy or was first cited on the death certificate; patients who underwent preoperative irradiation; patients with evidence of multiple resections within 6 months of diagnosis; patients with an unknown month of diagnosis; patients who were enrolled in a managed care organization any time from 6 months prior to cancer diagnosis to 3 years after diagnosis (because Medicare files do not include insurance claims data on managed care enrollees); and patients with a previous history of cancer; and patients with an unknown number of nodes evaluated (Appendix 9).

*Lymph Node Evaluation*

SEER routinely records the number of nodes pathologically examined for each patient as well as the presence and number of positive lymph nodes (as a continuous measure). We categorized patients according to their receipt (yes/no) of adequate lymph node evaluation (at least 12 nodes evaluated).

***Post-Surgical Treatment***

*Date of Surgical Resection*

We used the MedPAR date of surgical resection to determine receipt of recommended post-surgical care within the specified time-period after surgery for each guideline. We defined the date of surgical resection as the date corresponding to the radical resection codes in the

MedPAR file (Appendix 8). As invasive colon cancer requires an average hospital stay of 5-10 days,[63] the MedPAR file captures the majority of Medicare eligible fee-for-service patients undergoing colon cancer resection.[64-65]

*Receipt of Adjuvant Chemotherapy*

We classified patients as having received adjuvant chemotherapy (yes/no) if we found any claims-based evidence of chemotherapy administration or drug codes in the Medicare claims (NCH, Outpatient or MedPAR) within six months of diagnosis (see Appendix 10 for a complete list of codes). Based on previous studies evaluating chemotherapy in SEER-Medicare, we determined that one or more paid claims for chemotherapy was sufficient evidence to determine that a patient had undergone chemotherapy.[66] However, we extended the observation period to 6 months (2 months longer than guideline recommendations) to allow for potential coordinating efforts or post-surgical tests that might delay treatment initiation.

*Guideline Recommended Post-surgical Care*

Clinical practice guidelines from gastroenterology, oncology and surgery all advocate for routine follow-up and surveillance care after potentially curative resection for colon cancer.[43-46] While the exact timing and interval for recommended post-surgical care varies slightly by organization (Table 7), the majority of guidelines recommend some form of post-surgical surveillance and follow-up care in the 3 years after surgical treatment (Table 7). We selected three commonly recommended post-surgical guidelines for care after surgical resection (surveillance colonoscopy, computed tomography (CT) scan of the chest or abdomen, and carcinoembryonic antigen(CEA) testing) and searched for claims-based evidence of each in the 3 years after diagnosis (yes/no).

*Statistical Analysis*

We evaluated the unadjusted association between adequate lymph node evaluation (>12 nodes examined), patient and tumor factors, and receipt of post-surgical care using chi-square tests. We then used logistic regression to identify the association between guideline-recommended lymph node evaluation and receipt of 1) chemotherapy within 6 months of diagnosis and 2) post-surgical surveillance (surveillance colonoscopy, CT scan, and CEA testing), each within 3 years of surgical treatment. Finally, we used Kaplan Meier methods and Cox proportional hazards modeling to evaluate the relationship between adequate lymph node evaluation and 10-year overall hazard of death. We evaluated predictors of mortality among all patients and those who survived at least 3 years, remaining eligible for care during the entire observation period. All multivariate models used patients as the unit of analysis and were adjusted for age at diagnosis (66-69, 70-74, 75-79, 80-84, ≥85), race (White, Black, Other), sex, Charlson score[67-68] (0, 1, ≥2), tumor extent (T-stage[53] I-IV), grade, tumor location (proximal, distal), year of diagnosis, and registry.

We performed several sensitivity analyses to evaluate if the association between adequate lymph node evaluation, receipt of post-surgical care and mortality varied depending on modeling assumptions. Recognizing that the relationship between lymph node evaluation, receipt of post-surgical care and mortality may vary by how evaluation and post-surgical care were defined, we evaluated this relationship using different cut-points for lymph node evaluation (0, 1-8, 9-11, 12-15, 16-19, 20-29, 30-39, ≥40 nodes [Appendices 12a and b]) and the timeline for receipt of post-surgical care (within 1 [Appendix 13] and 5 years [Appendix 14]). Additionally, we recognized that the relationship between lymph node evaluation, receipt of post-surgical care and mortality may be highly correlated or impact survival differently among patient risk-factors or subgroups. We therefore performed several sensitivity analyses evaluating potential interactions between

lymph node count, age at diagnosis, tumor grade, T-stage to identify whether the association between lymph nodes, post-surgical care and mortality varied by these factors [Appendices 15 and 16]. Additionally, as the number of lymph nodes evaluated is highly correlated with the number of positive nodes identified [Appendix 17], we evaluated the association between lymph node evaluation and our outcomes adjusting for the number of positive nodes identified [Appendices 18 and 19]. Finally, we evaluated the association between lymph node evaluation, receipt of each type of post-surgical care and relative hazard of death separately in a series of models [Appendix 20]. Under all assumptions, our conclusions about the association between lymph node evaluation, receipt of post surgical care and relative hazard of death remained unchanged. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). All comparisons were pre-planned with p-values of $\leq 0.05$ considered significant.

**Results**

Among 17,906 surgically treated stage III colon cancer patients, we found that younger (55.1% of 66-69 year olds vs. 50.4% of >80 year olds), white patients (53.6% White vs. 50.9% Black) and those with lower levels of comorbidites were all more likely to receive adequate lymph node-evaluation (Table 8). Further, patients with more extensive bowel penetration (e.g., more extensive T-stage) and high-grade disease were more likely to receive adequate lymph node evaluation ($p<0.05$ for all), indicating that healthier patients and those at a higher risk of node positivity were the same patients who received more extensive nodal evaluation.

*Receipt of Guideline-Recommended Post-Surgical Care*

We found higher unadjusted rates of adjuvant chemotherapy receipt (56.1% vs. 52.6%; ≥12 LNs evaluated vs. < 12), CT scans (69.4% vs. 64.7%), CEA testing (74.5% vs. 68.8%) and surveillance colonoscopy (49.6% vs. 47.2%) among patients receiving adequate lymph node evaluation (Table 9). Limiting our evaluation to only those patients who survived to the end of the eligibility period for receipt of post-surgical care (e.g., 6-month and 3-year survivors), we

found no significant differences in the proportion of patients who underwent colonoscopy by level of lymph node evaluation. However, patients with adequate lymph node evaluation were still more likely to receive adjuvant chemotherapy, CT scans and CEA testing ($p<0.05$ for all).

Adjusting for tumor and patient factors, patients who received adequate lymph node evaluation were also more likely to receive recommended post-surgical care (adjuvant chemotherapy, CEA testing, and colonoscopy), with the exception of CT scans (Tables 10a and 10b). However, among patients who survived to the end of the eligibility period for post-surgical care, we found that individuals with adequate lymph node evaluation were no more likely to receive recommended post-surgical care than those with <12 nodes evaluated ($p>0.05$ for all). At the same time, several other patient and tumor factors remained consistent predictors of receiving post-surgical care including younger age, lower comorbidity score and lower T-stage at diagnosis (for receipt of CT scans and CEA testing only).

*10-Year Mortality*

Unadjusted Kaplan-Meier mortality estimates showed significantly lower 10-year overall mortality among patients who had adequate lymph node evaluation (Figure 4). Among 3-year survivors who were eligible for post-surgical care during the entire period, we continued to observe significantly lower unadjusted mortality among those with ≥12 lymph nodes evaluated (Figure 5). After adjusting for receipt of post-surgical care, we found that, at the time of surgical treatment, adequate lymph node evaluation was associated with lower relative hazard of death (adjusted hazard ratio (HR): 0.88; 95% Confidence Interval (0.85-0.91) ≥12 LNs vs. <12 LNs evaluated). However, the association between lymph node evaluation and mortality lessened the longer patients survived after surgery (Table 11). Among 3-year survivors, adequate lymph node evaluation was no longer associated with significantly lower 10-year hazard of death (HR:0.94; 95% CI (0.88-1.01), ≥12 LNs vs. <12 LNs evaluated). At the same time, in these 3-year

survivors, receiving recommended post-surgical care was still associated with significantly lower 10-year hazard of death, with the exception of those receiving CT scans.

We found a significant interaction between receipt of CT scans and comorbidity score at diagnosis indicating that the effect of receiving this care on mortality varied by how healthy patients were at diagnosis (Appendix 21). When stratified by comorbidity score, patients with low comorbidity scores (e.g., Charlson score $\leq 1$) did have significantly lower mortality given they received a CT scan; however, sicker patients (e.g. Charlson comorbidity score $\geq 3$) experienced higher mortality than those without the scan (See Appendix 22 for results). As Medicare claims do not provide a reason for the scan, these patients likely received CT scans due to the presence of post-operative symptoms or had other competing illnesses that may have contributed to less aggressive surgical care or adjuvant therapy. While adequate lymph node evaluation was not significantly associated with lower mortality after 3 years, other factors remained significantly associated with lower 10-year mortality including age at diagnosis, sex, T-stage, tumor location and comorbidity score.

**Discussion**

In our study of 17,906 surgically treated AJCC stage III colon cancer patients, we found that patients receiving adequate lymph node evaluation were initially more likely to receive recommended post-surgical care. However, for patients who survived at least 3 years after surgical treatment, we found patients who received adequate lymph node evaluation were no more likely to receive recommended post-surgical care. This suggests that high-quality surgical care does not necessarily lead to receipt of long-term follow-up care for colon cancer. Further, we found that while adequate lymph node evaluation was associated with lower 10-year hazard of death at the time of treatment. After patients survived 3 years, the association between lymph node evaluation and lower hazard of death was no longer significant; however, post-surgical care

remained strongly associated with lower long-term mortality indicating that post-surgical care may partially explain the relationship between lymph node evaluation and mortality.

Our results are consistent with several studies that show that availability of high-quality medical care among patients diagnosed with chronic disease does not necessarily translate into the continued availability or use of recommended services. While the reasoning behind non-adherence to recommended care for monitoring and control of chronic diseases is multi-factorial, several studies have demonstrated that insurance,[69-70] socioeconomic and tumor factors[70-71] and health-provider characteristics[72] all play a role in the continued access and use of recommended services. In a small study of surgically treated colorectal cancer patients, Elston-Lafata et al. found significant differences by race, income and tumor characteristics of patients who received CEA testing and colon examinations among insured patients in a managed care organization.[73] Our study builds upon these previous findings, identifying that access to high-quality surgical care and insurance coverage (i.e., Medicare) for recommended post-surgical care does not necessarily translate into higher use of those services. Therefore, future work should focus on the most effective system-wide interventions to encourage older, non-white patients and those with worse tumor prognosis (e.g., higher grade or T-stage) to undergo recommended post-surgical care as we demonstrate the important long-term benefits of this care on lower mortality across all patients.

Our results also provide further insight into the evolving nature of risk factors as patients survive longer with their disease. Several studies have demonstrated the strong influence that lymph node evaluation has on lower mortality across patient demographic and tumor characteristics at the time of surgical treatment.[6] In addition to lymph nodes, tumor characteristics such as higher T-stage and grade, as well as patient age and level of comorbidities predict long-term mortality when patients are first treated.[6] However, while tumor and demographic characteristics continue to provide prognostic information about long-term mortality after patients

survive several years with their disease, we found that lymph node evaluation is no longer associated with lower mortality among 3-year survivors, once adjusted for post-surgical care. At the same time, receiving recommended post-surgical care continues to provide long-term benefits of lower mortality among these 3-year survivors. These findings complement an emerging literature on the changing risk factors for long-term mortality as patients survive longer after their initial cancer diagnosis. Currently most clinicians use the American Joint Committee on Cancer (AJCC) staging system and prognostic modeling to develop survival estimates for patients after diagnosis, relying primarily on histological subtype, tumor grade, size, depth, and the presence of distant or nodal metastases at the time of diagnosis or treatment.[8] However, previous studies of other cancers have demonstrated that the ability of some patient and tumor factors to predict survival may decrease over time, depending on patients' current survival period.[74-78] As a result, evaluating the changing impact of guideline recommended lymph node evaluation combined with post-surgical care as patients survive longer with their disease may provide more meaningful information to aid clinical decision management. Our study suggests that while lymph node evaluation does provide important initial information about mortality risk, the long-term benefits of more extensive lymph node evaluation may be due to the receipt of post-surgical care. Therefore, policy-makers and providers should examine best-practices for promoting continued use of recommended cancer treatment and post-surgical care after the initial survival period.

While our study provides results from a large nationally-representative dataset, we acknowledge several data-related limitations. First, SEER-Medicare data are limited to patients over the age of 65 (66 to adjust for comorbidities in the year prior to diagnosis). As a result, our conclusions may not be generalizable to younger colon cancer survivors. However, between 2003 and 2007, the median age at diagnosis for cancer of the colon or rectum was 70 years of age.[48] Therefore, the analysis should capture a large portion of the population diagnosed with colon cancer in SEER geographic areas. Additionally, Medicare data represent administrative data

collected for billing purposes rather than research. For this reason, our analysis was constructed to identify commonly billed procedures from a cohort of patients likely to have complete claims (i.e. surgical resection according to SEER, FFS in the six months prior to six months post diagnosis). Third, we are unable to distinguish between surveillance colonoscopy and symptom-driven colonoscopy among patients. Finally, while health maintenance organizations may impact the receipt of specific types of post-surgical care, Medicare HMOs do not submit claims-based data forms that are released to researchers. Therefore, our analysis was limited to the fee-for-service population and is generalizable to this specific subset of the Medicare population. However, SEER-Medicare allows for the analysis of a population-based set of cancer registries that includes patients from diverse backgrounds and practices from throughout the United States. Additionally, Medicare is the largest form of health insurance in the US population, making this study broadly applicable to a large population of elderly colon cancer patients.

These findings provide several important implications for the use of lymph node evaluation as a quality-indicator for colon cancer care. First, our findings suggest that more extensive lymph node evaluation does provide important survival benefits in the initial years after surgical treatment. Considering that the evaluation of lymph nodes during surgical resection for colon cancer is not onerous, future guidelines should continue to promote evaluation as a combined approach to decrease long-term mortality in this population. Additionally, our findings should stimulate future work to identify other clinical and molecular markers that may present additional insight into the mechanism between lymph node evaluation and lower mortality directly after treatment. Finally, our findings point toward the continued need to encourage patients to maintain recommended surveillance and post-surgical care after their initial surgical treatment to maximize the benefits of high quality surgical care for colon cancer.

In conclusion, we found that adequate lymph node evaluation is associated with lower mortality directly after surgical treatment, while post-surgical care is more strongly associated

with lower mortality after patients survive 3 years. However, patients who receive adequate lymph node evaluation are no more likely to receive recommended post-surgical care despite the combined long-term benefits lower mortality with this combined care approach. Policy-makers and providers should examine best-practices for promoting continued use of recommended cancer treatment and post-surgical care among cancer survivors and incorporation of these services into survivorship programs.

**Table 7: Adjuvant Therapy and Surveillance Guidelines for AJCC Stage III[42] Colon Cancer, by Recommending Organization**

| Test | National Comprehensive Cancer Network (NCCN)[13, 44] | American Society for Clinical Oncology (ASCO)[13, 43-44] | US Multi-Society Task Force on Colorectal Cancer (USMTF)[45] | Gastrointestinal Consortium Panel[46] |
|---|---|---|---|---|
| *Chemotherapy* | Adjuvant chemotherapy within 4 months for patients <80 years at diagnosis with AJCC Stage III (i.e. lymph node positive) colon cancer | Adjuvant chemotherapy within 4 months for patients <80 years at diagnosis with AJCC Stage III (i.e. lymph node positive) colon cancer | | |
| *Surveillance Colonoscopy* | Within 1 year of diagnosis, unless no preoperative colonoscopy due to obstruction; then perform within 3-6 months; If advance adenoma repeat in 1 year; If not advanced adenoma; repeat in 3 years; then every 5 years | If complete preoperative colonoscopy, at 3 years; If results are normal, every 5 years. | If complete pre-operative colonoscopy performed, then at 1 year. If normal, repeat in 3 years. If second colonoscopy is normal, repeat in 5 years. | If no pre-operative colonoscopy, colonoscopy at 6 months after surgery; If normal, colonoscopy at 3 years; If second colonoscopy is normal, repeat in 5 years. |
| *Computed tomography scan of the chest/abdomen* | Every year for 3 years for patients with high risk of recurrence (e.g. lymphatic invasion or poorly differentiated tumors) | Every year for 3 years if stage III disease or high-risk stage II | | |
| *Carcinoembryonic antigen Test* | Every 3-6 months for 2 years; then every 6 months for a total of 5 years for T-stage 2 or higher tumors | Every 3 months for at least 3 years in patients with stage II or III disease | | |

AJCC: American Joint Committee on Cancer

**Table 8: Patient Tumor and Demographic Characteristics by Level of Lymph Node (LN) Evaluation for Colon Cancer, AJCC Stage III Patients (N=17,906 )**

| | <12 LN (N=8,374) | ≥12 LN (N=9,532) | Total N | P-Value |
|---|---|---|---|---|
| **Age** | | | | 0.004 |
| 66-69 | 44.9 (1,168) | 55.1 (1,430) | 2,598 | |
| 70-74 | 46.0 (1,807) | 54.0 (2,119) | 3,926 | |
| 75-79 | 46.3 (2,018) | 53.7 (2,342) | 4,360 | |
| 80-84 | 46.8 (1,737) | 53.2 (1,971) | 3,708 | |
| ≥85 | 49.6 (1,644) | 50.4 (1,670) | 3,314 | |
| **Race** | | | | 0.01 |
| White | 46.4 (7,067) | 53.6 (8,150) | 15,217 | |
| Black | 48.1 (674) | 51.9 (726) | 1,400 | |
| Other/Unknown | 49.1 (633) | 50.9 (656) | 1,289 | |
| **Sex** | | | | 0.0004 |
| Male | 48.4 (3,582) | 51.6 (3,827) | 7,409 | |
| Female | 45.7 (4,792) | 54.3 (5,705) | 10,497 | |
| **Charlson Comorbidity Score** | | | | |
| 0 | 45.8 (5,118) | 54.2 (6,060) | 11,178 | <0.001 |
| 1 | 45.8 (1,463) | 54.2 (1,730) | 3,193 | |
| 2 | 49.5 (838) | 50.5 (856) | 1,694 | |
| ≥3 | 51.9 (955) | 48.1 (886) | 1,841 | |
| **T-Stage** | | | | <0.001 |
| 1 | 64.4 (271) | 35.6 (150) | 421 | |
| 2 | 52.5 (758) | 47.5 (686) | 1,444 | |
| 3 | 45.6(5,737) | 54.5 (6,859) | 12,596 | |
| 4 | 46.7 (1,608) | 53.3 (1,837) | 3,445 | |
| **Tumor Location** | | | | <0.001 |
| Proximal Colon | 42.3 (5,379) | 57.7 (7,332) | 12,711 | |
| Distal Colon | 57.7 (2,995) | 42.4 (2,200) | 5,195 | |
| **Grade** | | | | <0.001 |
| Well/Moderately Differentiated | 47.9 (5,797) | 52.1 (6,311) | 12,108 | |
| Poorly/Undifferentiated | 44.5 (2,577) | 55.5 (3,221) | 5,798 | |

**Table 9: Proportion of Stage III Colon Cancer Patients Receiving Guideline-Recommended Care, by Level of Lymph Node Evaluation (N=17,906), % (N)***

| Recommended Care | <12 LN (N=8,374) | ≥12 LN (N=9,532) | P-Value |
|---|---|---|---|
| ***Adjuvant Chemotherapy*** | | | |
| Chemotherapy Receipt within 6 months of Diagnosis (all patients) | 52.6 (4,406) | 56.1 (5,350) | p<0.001 |
| Chemotherapy Receipt within 6 months of Diagnosis (6-month survivors) | 59.3 (4,232 of 7,141) | 61.3 (5,171 of 8,440) | p=0.01 |
| ***Surveillance Colonoscopy*** | | | |
| Colonoscopy within 3 years of Surgical Treatment (all patients) | 47.2 (3,956) | 49.6 (4,729) | p=0.002 |
| Colonoscopy within 3 years of Surgical Treatment (3-year survivors) | 69.8 (3,074 of 4,406) | 68.7 (3,852 of 5,610) | p=0.20 |
| ***Computed Tomography (CT) Scan*** | | | |
| CT Scan of the Chest or Abdomen within 3 years of Surgical Treatment (all patients) | 64.7 (5,420) | 69.4 (6,661) | p<0.001 |
| CT Scan of the Chest or Abdomen within 3 years of Surgical Treatment (3-year survivors) | 69.5 (3,064 of 4,406) | 72.3 (4,058 of 5,610) | p=0.002 |

**Table 9 (Continued): Proportion of Stage III Colon Cancer Patients Receiving Guideline-Recommended Care, by Level of Lymph Node Evaluation (N=17,906), % (N)***

| **Recommended Care** | <12 LN (N=8,374) | ≥12 LN (N=9,532) | P-Value |
|---|---|---|---|
| ***Carcinoembryonic Antigen (CEA) Test*** | | | |
| Any CEA Test within 3 years of Surgical Treatment (all patients) | 68.8 (5,757) | 74.5 (7,101) | p<0.001 |
| Any CEA Test within 3 years of Surgical Treatment (3-year survivors) | 85.1 (3,751 of 4,406) | 88.2 (4,945 of 5,610) | p<0.001 |

*Chi-square test

**Table 10a: Predictors of Guideline Recommended Post-Surgical Care for AJCC Stage III Colon Cancer Patients*, Adjusted Odds Ratio (95% CI)**

| | | Chemotherapy Receipt within 6 Months of Diagnosis | | Colonoscopy within 3 Years of Surgical Treatment | |
|---|---|---|---|---|---|
| | | All Patients (N=17,906) | 6 Month Survivors (N= 15, 581) | All Patients (N=17,906) | 3 Year Survivors (N=10,016) |
| **LNs Evaluated** | | | | | |
| | <12 | Ref | Ref | Ref | Ref |
| | ≥12 | 1.09 (1.02, 1.17) | 1.01 (0.94, 1.10) | 1.12 (1.05, 1.20) | 0.98 (0.89, 1.08) |
| | | | | | |
| **Age** | 66-69 | Ref | Ref | Ref | Ref |
| | 70-74 | 0.65 (0.58, 0.74) | 0.68 (0.59, 0.78) | 0.81 (0.73, 0.89) | 0.88 (0.75, 1.05) |
| | 75-79 | 0.38 (0.33, 0.42) | 0.37 (0.33, 0.43) | 0.59 (0.54, 0.66) | 0.70 (0.60, 0.81) |
| | 80-84 | 0.14 (0.12, 0.16) | 0.13 (0.12, 0.15) | 0.36 (0.32, 0.39) | 0.39 (0.34, 0.46) |
| | ≥85 | 0.03 (0.03, 0.04) | 0.03 (0.03, 0.04) | 0.15 (0.13, 0.17) | 0.17 (0.15, 0.20) |
| **Sex** | Female | Ref | Ref | Ref | Ref |
| | Male | 1.13 (1.05, 1.21) | 1.18 (1.09, 1.27) | 1.00 (0.94, 1.07) | 1.03 (0.94, 1.13) |
| **Race** | White | Ref | Ref | Ref | Ref |
| | Black | 0.51 (0.45, 0.59) | 0.51 (0.44, 0.59) | 0.69 (0.61, 0.78) | 0.63 (0.53, 0.74) |
| | Other/Unknown | 0.94 (0.81, 1.09) | 0.86 (0.73, 1.01) | 0.97 (0.85, 1.12) | 0.82 (0.69, 0.98) |
| **Charlson Score** | | | | | |
| | 0 | Ref | Ref | Ref | Ref |
| | 1 | 0.76 (0.69, 0.83) | 0.78 (0.71, 0.87) | 0.83 (0.76, 0.90) | 0.89 (0.79, 1.00) |
| | 2 | 0.66 (0.59, 0.74) | 0.68 (0.59, 0.77) | 0.74 (0.66, 0.83) | 0.88 (0.75, 1.04) |
| | ≥3 | 0.36 (0.32, 0.41) | 0.39 (0.35, 0.45) | 0.48 (0.43, 0.54) | 0.66 (0.56, 0.78) |
| **Tumor Location** | | | | | |
| | Proximal | Ref | Ref | Ref | Ref |
| | Distal | 0.95 (0.88, 1.03) | 0.97 (0.89, 1.05) | 1.06 (0.98, 1.13) | 0.94 (0.85, 1.04) |
| **Grade** | | | | | |
| | Well/Moderately Differentiated | Ref | Ref | Ref | Ref |
| | Poorly/Undifferentiated | 0.99 (0.92, 1.07) | 0.92 (0.85, 0.99) | 1.26 (1.18, 1.35) | 1.11 (1.00, 1.22) |
| **T-stage** | | | | | |
| | 1 | Ref | Ref | Ref | Ref |
| | 2 | 0.84 (0.65, 1.09) | 0.88 (0.67, 1.16) | 0.85 (0.67, 1.08) | 0.99 (0.74, 1.32) |
| | 3 | 0.68 (0.53, 0.86) | 0.77 (0.60, 0.99) | 0.53 (0.42, 0.65) | 0.59 (0.42, 0.99) |
| | 4 | 0.56 (0.44, 0.71) | 0.72 (0.55, 0.93) | 0.31 (0.24, 0.39) | 0.64 (0.48, 0.85) |
| | C-Index | 0.79 | 0.79 | 0.71 | 0.68 |
| * Also adjusted for registry and year of diagnosis | | | | | |

**Table 10b: Predictors of Guideline Recommended Post-Surgical Care for AJCC Stage III Colon Cancer Patients*, Adjusted Odds Ratio (95% CI)**

| | | Computed Tomography (CT) Scan of the Chest or Abdomen within 3 Years of Surgical Treatment | | Carcinoembryonic Antigen (CEA) Test within 3 years of Surgical Treatment | |
|---|---|---|---|---|---|
| | | All Patients (N=17,906) | 3 Year Survivors (N=10,016) | All Patients (N=17,906) | 3 Year Survivors (N=10,016) |
| **Lymph Nodes Evaluated** | | | | | |
| | <12 | Ref | Ref | Ref | Ref |
| | ≥12 | 1.05 (0.98, 1.13) | 0.96 (0.87, 1.05) | 1.09 (1.02, 1.16) | 1.12 (0.99, 1.27) |
| | | | | | |
| **Age** | 66-69 | Ref | Ref | Ref | Ref |
| | 70-74 | 0.81 (0.72, 0.92) | 0.87 (0.75, 1.02) | 0.89 (0.80, 0.99) | 0.67 (0.52, 0.85) |
| | 75-79 | 0.63 (0.56, 0.70) | 0.68 (0.59, 0.79) | 0.74 (0.67, 0.82) | 0.52 (0.41, 0.66) |
| | 80-84 | 0.42 (0.37, 0.47) | 0.43 (0.37, 0.50) | 0.46 (0.41, 0.51) | 0.27 (0.22, 0.35) |
| | ≥85 | 0.19 (0.17, 0.22) | 0.21 (0.17, 0.25) | 0.21 (0.19, 0.24) | 0.10 (0.08, 0.13) |
| **Sex** | Female | Ref | Ref | Ref | Ref |
| | Male | 0.98 (0.92, 1.05) | 1.03 (0.94, 1.13) | 1.07 (1.01, 1.14) | 1.12 (0.98, 1.27) |
| **Race** | | | | | |
| | White | Ref | Ref | Ref | Ref |
| | Black | 0.86 (0.76, 0.98) | 0.85 (0.70, 1.02) | 0.77 (0.68, 0.87) | 0.67 (0.53, 0.85) |
| | Other/Unknown | 1.17 ( 1.01, 1.35) | 1.06 (0.87, 1.28) | 1.12 (0.98, 1.29) | 0.83 (0.64, 1.08) |
| **Charlson Score** | | | | | |
| | 0 | Ref | Ref | Ref | Ref |
| | 1 | 0.92 (0.84, 1.01) | 1.09 (0.96, 1.24) | 0.97 (0.89, 1.06) | 1.06 (0.89, 1.26) |
| | 2 | 0.95 (0.84, 1.06) | 1.11 (0.93, 1.31) | 0.99 (0.89, 1.11) | 0.80 (0.65, 0.99) |
| | ≥3 | 0.75 (0.67, 0.83) | 1.13 (0.94, 1.37) | 0.63 (0.56, 0.69) | 0.52 (0.42, 0.64) |
| **Tumor Location** | | | | | |
| | Proximal | Ref | Ref | Ref | Ref |
| | Distal | 0.89 (0.83, 0.96) | 0.98 (0.88, 1.08) | 0.94 (0.87, 1.01) | 0.91 (0.79, 1.05) |
| **Grade** | | | | | |
| | Well/Moderately Differentiated | Ref | Ref | Ref | Ref |
| | Poorly/Undifferentiated | 1.02 (0.95, 1.10) | 1.06 (0.95, 1.17) | 1.01 (0.95, 1.09) | 0.99 (0.87, 1.14) |
| **T-stage** | | | | | |
| | 1 | Ref | Ref | Ref | Ref |
| | 2 | 0.98 (0.77, 1.26) | 1.04 (0.78, 1.39) | 0.92 (0.73, 1.16) | 1.46 (0.99, 2.14) |
| | 3 | 1.06 (0.85, 1.33) | 1.12 (0.86, 1.45) | 0.79 (0.65, 0.98) | 1.24 (0.88, 1.74) |
| | 4 | 1.00 (0.79, 1.27) | 1.29 (0.97, 1.72) | 0.72 (0.58, 0.89) | 1.42 (0.98, 2.07) |
| | C-index | 0.68 | 0.70 | 0.69 | 0.74 |

* Also adjusted for registry and year of diagnosis

**Table 11: Factors Associated with 10-Year Relative Hazard of Death Among AJCC Stage III Colon Cancer Patients, Cox Proportional Hazard Models, Hazard Ratio, 95% CI**

| | All Patients (N=17,906) | | 3-Year Survivors (N=10, 016) | |
|---|---|---|---|---|
| | Model 1 | Model 2 | Model 3 | Model 4 |
| **Lymph Nodes Evaluated** | | | | |
| <12 | Ref | Ref | Ref | Ref |
| ≥12 | 0.86 (0.83, 0.89) | 0.88 (0.85, 0.91) | 0.94 (0.88, 0.99) | 0.94 (0.88, 1.01) |
| Guideline Recommended Post-Surgical Care | | | | |
| Chemotherapy within 6 months of diagnosis | | 0.82 (0.78, 0.86) | | 0.72 (0.67, 0.79) |
| Colonoscopy within 3 years of surgery | | 0.41 (0.39, 0.43) | | 0.68 (0.63, 0.73) |
| CT scan within 3 years of surgery | | 1.3 (1.25, 1.36) | | 1.58 (1.47, 1.71) |
| CEA within 3 years of surgery | | 0.49 (0.47, 0.52) | | 0.84 (0.76, 0.92) |
| Patient and Tumor Factors | | | | |
| **Age** | | | | |
| 66-69 | Ref | Ref | Ref | Ref |
| 70-74 | 1.26 (1.17, 1.35) | 1.17 (1.09, 1.26) | 1.36 (1.22, 1.52) | 1.32 (1.19, 1.48) |
| 75-79 | 1.46 (1.36, 1.56) | 1.25 (1.16, 1.33) | 1.55 (1.39, 1.73) | 1.48 (1.33, 1.65) |
| 80-84 | 1.92 (1.80, 2.05) | 1.33 (1.23, 1.42) | 2.16 (1.93, 2.42) | 1.86 (1.65, 2.09) |
| ≥85 | 2.83 (2.65, 3.04) | 1.47 (1.36, 1.58) | 3.25 (2.88, 3.65) | 2.46 (2.16, 2.79) |
| **Sex** | | | | |
| Female | Ref | Ref | Ref | Ref |
| Male | 1.14 (1.09, 1.18) | 1.17 (1.12, 1.21) | 1.33 (1.25, 1.42) | 1.35 (1.26, 1.44) |
| **Race** | | | | |
| White | Ref | Ref | Ref | Ref |
| Black | 1.13 (1.06, 1.22) | 0.99 (0.92, 1.06) | 1.10 (0.97, 1.25) | 1.02 (0.90, 1.16) |
| Other/Unknown | 0.87 (0.81, 0.95) | 0.83 (0.76, 0.90) | 0.88 (0.77, 1.01) | 0.85 (0.74, 0.97) |
| **Charlson Comorbidity Score** | | | | |
| 0 | Ref | Ref | Ref | Ref |
| 1 | 1.28 (1.22, 1.34) | 1.25 (1.19, 1.31) | 1.37 (1.26, 1.48) | 1.33 (1.22, 1.45) |
| 2 | 1.33 (1.25, 1.42) | 1.22 (1.14, 1.29) | 1.42 (1.27, 1.48) | 1.37 (1.23, 1.530 |
| ≥3 | 1.89 (1.78, 1.99) | 1.55 (1.46, 1.64) | 2.09 (1.87, 2.34) | 1.91 (1.71, 2.13) |
| **Tumor Location** | | | | |
| Proximal | Ref | Ref | Ref | Ref |
| Distal | 1.19 (1.15, 1.24) | 1.18 (1.13, 1.22) | 1.15 (1.07, 1.23) | 1.14 (1.06, 1.22) |
| **Grade** | | | | |
| Well/Moderately Differentiated | Ref | Ref | Ref | Ref |
| Poorly/Undifferentiated | 0.97 (0.93, 1.01) | 0.95 (0.91, 0.99) | 0.96 (0.90, 1.04) | 0.97 (0.90, 1.04) |
| **T-stage** | | | | |
| 1 | Ref | Ref | Ref | Ref |
| 2 | 1.27 (1.07, 1.50) | 1.31 (1.10, 1.55) | 1.22 (0.96, 1.55) | 1.25 (0.98, 1.60) |
| 3 | 1.97 (1.69, 2.31) | 1.85 (1.58, 2.16) | 1.61 (1.29, 2.00) | 1.59 (1.27, 1.98) |
| 4 | 3.06 (2.61, 3.59) | 2.66 (2.27, 3.12) | 1.94 (1.53, 2.45) | 1.88 (1.49, 2.37) |

* Also adjusted for registry and year of diagnosis

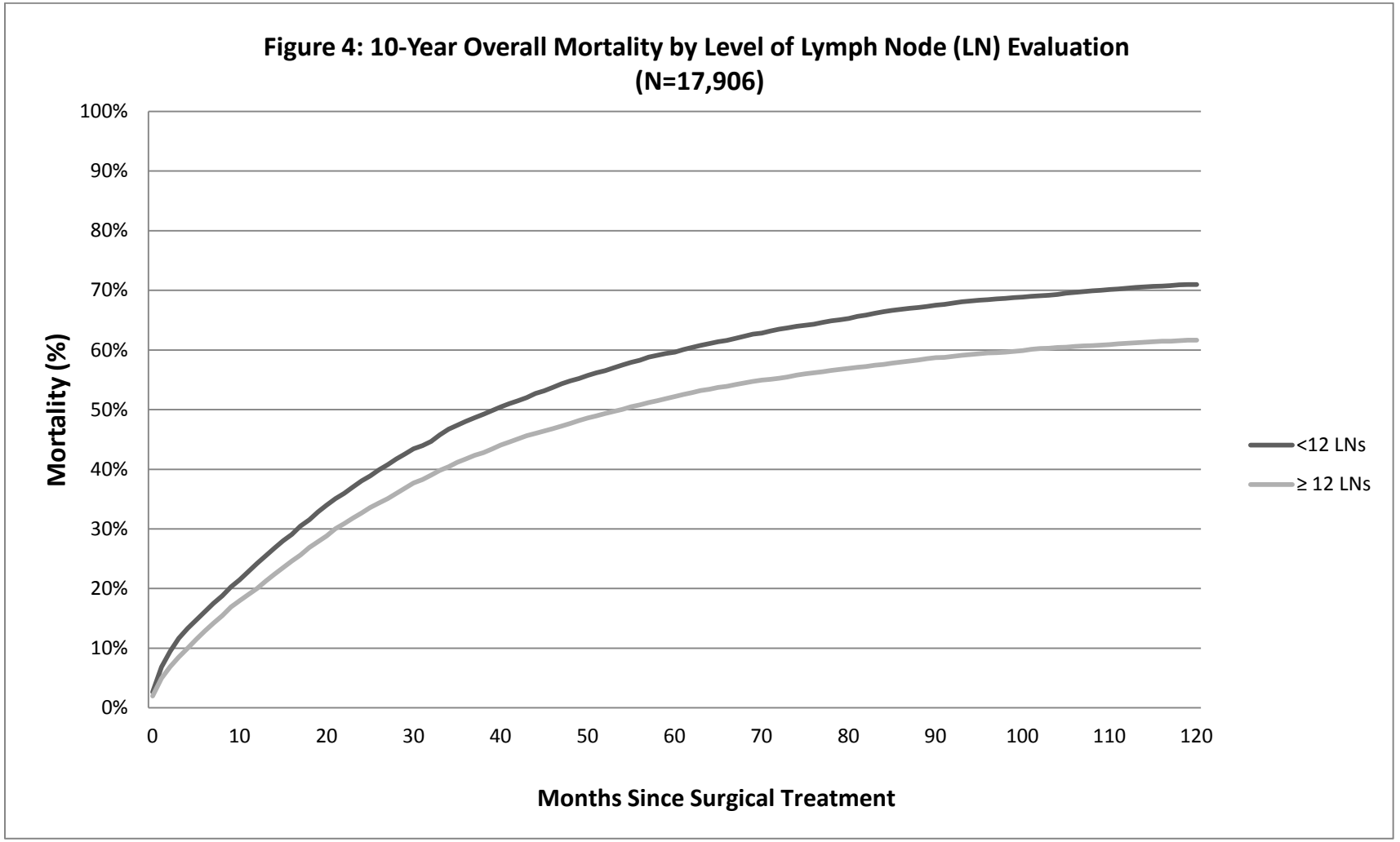
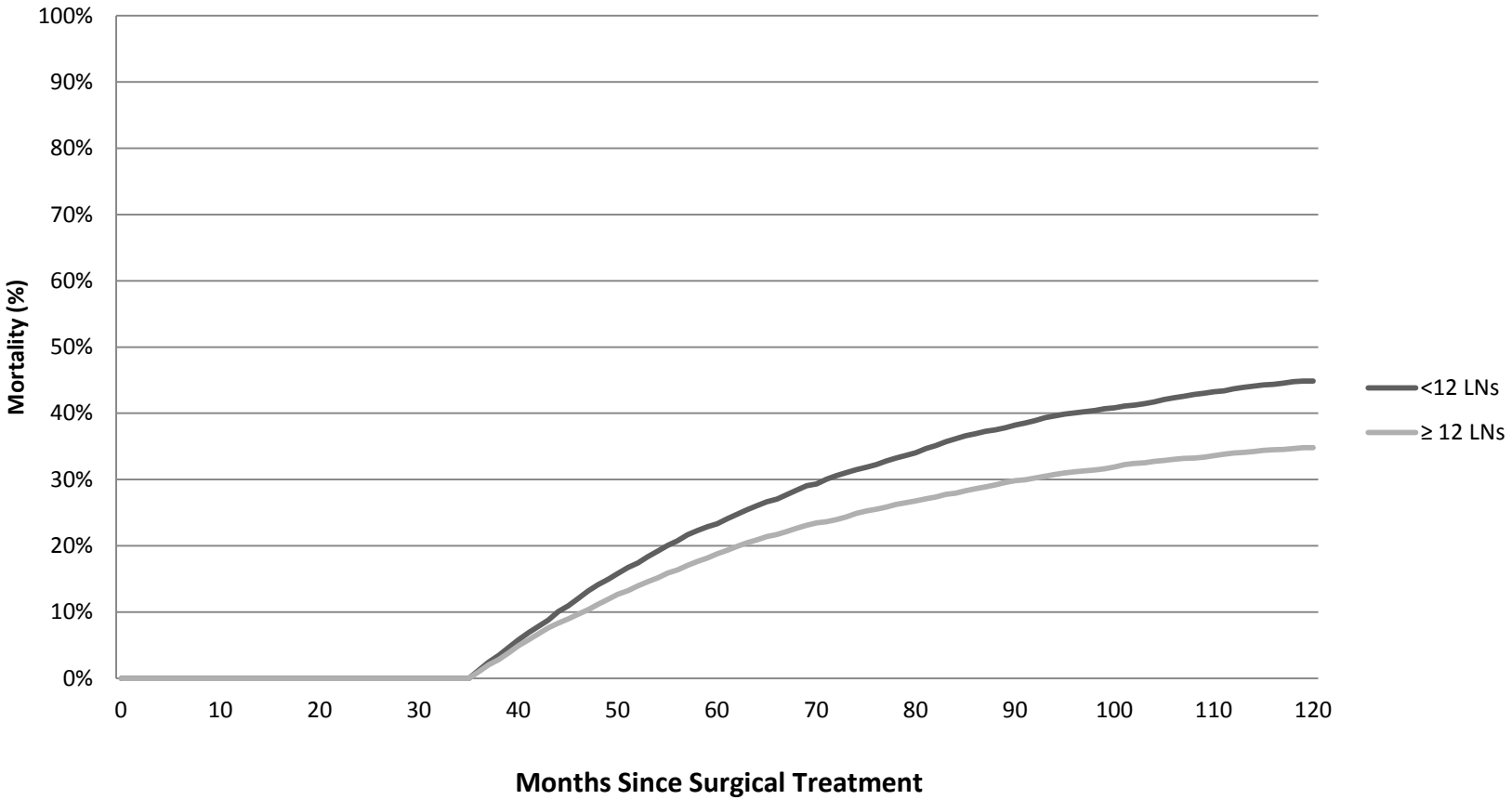


Figure 4: 10-Year Overall Mortality by Level of Lymph Node (LN) Evaluation
(N=17,906)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Mortality (%)
0
10
20
30
40
50
60
70
80
90
100
110
120
Months Since Surgical Treatment
<12 LNs
≥ 12 LNs

**Figure 5: 10-Year Conditional Mortality by Level of Lymph Node (LN) Evaluation, 3-Year Survivors (N=10,016)**



# Chapter 5: Hospital Characteristics Associated with Maintenance or Improvement of Guideline-recommended Lymph Node Evaluation for Colon Cancer

**Background:** Over the past 20 years, several surgical practice organizations have recommended the identification of ≥12 lymph nodes from surgically treated colon cancer patients as an indicator of quality performance for adequate staging; however, studies suggest that significant variation exists among hospitals in their level of adherence to this recommendation. We examined hospital-level factors that were associated with institutional improvement or maintenance of adequate lymph node evaluation after the introduction of surgical quality guidelines for colon cancer.

**Methods:** Using the 1996-2007 SEER-Medicare linked data, we evaluated hospital characteristics associated with short- (1996-1998 vs. 1999-2001), medium- (1996-1998 vs. 2002-2004), and long-term (1996-1998 vs. 2005-2005) improvement or maintenance of guideline-recommended lymph node evaluation (≥12 lymph nodes evaluated) using chi-square tests and multivariate logistic regression, adjusting for patient case-mix.

**Results:** We identified 228 hospitals that performed at least 6 colon cancer surgeries during each study period from 1996-2007. In the initial study period (1996-1998), 26.3% (n=60) of hospitals were performing guideline-recommended evaluation, increasing to 28.1% in 1999-2001, 44.7% in 2002-2004, and 70.6% in 2005-2007. In multivariate analyses, a hospital's prior guideline performance, teaching status and American College of Surgeon's Oncology Group membership were significantly associated with short and medium-term improvement or maintenance of guideline-recommended lymph node evaluation; however, these factors were not associated with long-term performance.

**Conclusions:** Over the 12 year period, there were significant improvements in hospital performance for guideline-recommended lymph node evaluation. Understanding where these improvements occur over time contributes to the debate over the optimal design of quality improvement programs.

**Background**

Several studies have identified an association between patients who have more lymph nodes evaluated during resection for colon cancer and improved survival.[6] As a result of these studies, several organizations including the National Comprehensive Cancer Network and the American Society for Clinical Oncology have recommended the evaluation of 12 or more lymph nodes from resected colon cancer patients as an indicator of quality performance.[13] The first guideline was issued in 1990 in the Working Party Report to the World Congress of Gastroenterology. Since 1997, the majority of surgical and oncology groups have recommended the evaluation of 12 or more lymph nodes during surgical resection for adequate staging. However, several studies have suggested that significant variation exists among hospitals in their level of adherence to this recommendation.[21, 28] Previous single-institution and population-based studies have examined characteristics of providers who adhere to these guidelines, finding that after accounting for patient demographics and tumor characteristics, the majority of modifiable variation in guideline-recommended evaluation occurs at the hospital level.[79]

Various approaches have been advocated to address the issue of inadequate lymph node evaluation. Increasingly, large payer organizations have begun to use lymph node evaluation guidelines to set pay-for-performance criterion. Specifically, the Centers for Medicare and Medicaid Services (CMS) has discussed the introduction of lymph node evaluation standards as a quality measure for pay-for-performance initiatives.[79] However, concern has been raised that the use of these guidelines may divert resources away from resources more likely to result in improved patient outcomes, particularly when the exact threshold for lymph node evaluation to improve survival remains in contention.[16, 22, 48] Additionally, studies have shown that underperforming hospitals are likely to remain so, despite concerted efforts to improve performance.[80] Better understanding of hospital factors that contribute to improvement in guideline-recommended evaluation will provide policy-makers, administrators and payers with

information to guide future resource planning and areas to focus future quality improvement efforts.

In this study, we address the issue of guideline compliance from an institutional perspective. Specifically, we examine hospital-level factors that are associated with institutional improvement or maintenance of guideline-recommended lymph node evaluation (median nodal evaluation ≥12) after the introduction of surgical quality guidelines for colon cancer in the 1990s.

**Methods**

Data

For this hospital-level analysis examining patterns of improvement or maintenance of guideline-recommended lymph-node evaluation over time, we used the 1996-2007 Surveillance, Epidemiology, and End Results (SEER) cancer registry data linked to Medicare enrollment records and utilization data (SEER-Medicare). SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the US population.[62] The SEER-Medicare Patient Entitlement and Diagnosis Summary File (PEDSF) includes patient characteristics, primary tumor site, tumor stage and grade, first course of treatment (including surgery and irradiation), follow-up for vital status, and number of lymph nodes pathologically examined.[64]

Medicare provides comprehensive health care for about 97% of the U.S. population aged 65 or older.[64] Cancer cases reported to SEER have been matched to the Medicare master enrollment file, in order to facilitate population-based health services research. Medicare eligibility has been identified for 93% of people 65 or older identified by SEER.[61, 64] For Medicare enrollees who do not participate in a managed care plan, claims data are available through the Medicare Provider Analysis and Review (MedPAR) file, the National Claims History (NCH) file, and the Outpatient SAF file. Claims for hospitalizations and inpatient procedures are

available in the MedPAR and NCH files, while office visits are captured through a combination of the NCH file for provider charges and the Outpatient SAF file for facility charges.[61]

In addition to the SEER data and Medicare claims, NCI maintains a hospital file of all providers in the SEER-Medicare data. The file includes the number of Medicare-certified hospital beds, location (urban vs. rural), teaching status, hospital ownership, NCI cancer center status, and specialty group affiliation (e.g., American College of Surgeon's Oncology Group [ACOSOG]). Most variables in the hospital file are abstracted from the Provider of Services (POS) and Healthcare Cost Report (HCRIS) files, which are maintained by the Center for Medicare and Medicaid Services (CMS). NCI additionally collects information for the hospital file on specialty group affiliation (e.g, ACOSOG) and NCI cancer center status. The hospital file is available for the years 1996, 2000, 2001, 2002, 2003, 2005, 2006, and 2007.[61]

Patients

Included in our study were surgically treated patients ages 66 to 90 who were diagnosed with invasive, non-metastatic adenocarcinoma of the colon from January 1, 1996, through December 31, 2007. We included only patients who underwent radical resection for colorectal cancer (partial colectomy, hemicolectomy, total colectomy, total proctocolectomy, or coloproctotectomy) as the first course of treatment according to SEER.

Excluded from the study were patients with in situ, metastatic, or unstaged cancers; patients whose cancer was diagnosed by autopsy or first cited on the death certificate; patients who underwent preoperative irradiation; patients who were enrolled in a managed care organization any time from 6 months prior to cancer diagnosis (because Medicare files do not include insurance claims data on managed care enrollees) to 6 months post-diagnosis or death; patients with a previous history of cancer; and patients with an unknown number of nodes evaluated (See Appendix 23).

Hospitals

In order to evaluate hospital-level factors associated with improvement or maintenance of guideline-recommended lymph node evaluation, we restricted the analysis to hospitals that treated patients during each of the time periods in our study (1996-1998, 1999-2001, 2002-2004 and 2005-2007). Further, we restricted the analysis to only hospitals that performed at least 6 surgeries during each of the 3 year study periods (i.e., performing on average at least two surgeries per year) to ensure the effect of hospital characteristics on performance was not due to the characteristics of a single patient or a small group of patients. Based on these criteria we identified a cohort of older colon cancer patients, in which each patient was linked with a single hospital during one of the time-periods included in the study.

Identifying Hospital-Level Improvement or Maintenance of Guideline-Recommended Lymph Node Evaluation

We evaluated short (1999-2001), medium (2002-2004) and long (2005-2007) term improvement or maintenance in guideline-recommended lymph node evaluation at the hospital level. We categorized hospitals as performing guideline-recommended lymph node evaluation if the median lymph node count during a study period was ≥12 (yes or no).

Hospital-Level Measures

Hospital-level measures used in the analyses were identified from a combination of information included in the SEER-Medicare hospital file and Medicare claims. In order to identify initial factors associated with improvement or maintenance of guideline-recommended lymph node evaluation, we focused on hospital factors in the initial study period (1996-1998). Using the 1996 and 1998 Hospital files, we created a combined measure of teaching hospital status, based on presence of an American Medical Association-approved residency program (yes/no) in the hospital. We collapsed the categories of hospital ownership (non-profit, for-profit,

and government) and number of hospital beds (<200, 200-299, 300-399, >400) to allow for a sufficient number of hospitals in each category, while NCI cancer center status and ACOSOG membership were left unchanged. Finally, using the unique hospital identifier in the Medicare claims, we identified hospital volume of colorectal cancer radical resection procedures (in quartiles) for the initial study period (1996-1998) among patients included in our study.

Statistical Analysis

We evaluated the unadjusted differences between demographic and hospital characteristics and guideline-recommended lymph node evaluation on a hospital level using chi-square analyses. We then used multivariate logistic regression to evaluate the relationship between hospital characteristics and short, medium or long-term improvement or maintenance in guideline-recommended lymph node evaluation (yes vs. no) after adjusting for the case-mix of patients within facilities. Hospital characteristics included in the multivariate models included teaching hospital status/presence of an AMA approved residency program, hospital ownership, hospital volume, hospital location, and ACOSOG membership. Patient characteristics included the percentage of patients ≥80 years of age, the percentage of non-white patients, the percentage of male patients, the percentage of proximal tumors, the percentage of high grade tumors, the percentage of patients with a high Charlson score (≥3), and the percentage of high staged (AJCC Stage III) cancers treated by the hospital in each study period compared. For all statistical analyses, we used SAS software, version 9.2 (SAS Institute Inc., Cary, NC). P values $\leq 0.05$ were considered statistically significant.

Results

We identified 228 hospitals that surgically treated 24,926 patients for non-metastatic colon cancer between1996-2007 and performed at least 6 procedures in each study period. Over time, the distribution of patients in the hospital cohort shifted to patients more likely to be older at

diagnosis, non-white, and presenting with more advanced AJCC stage at diagnosis (Table 12). Further, over time, patients were more likely to be diagnosed with proximal tumors and have higher levels of comorbidity; however, no differences existed in patient sex or tumor grade over time.

In the initial study period (1996-1998), 26.3% (n=60) of hospitals performed guideline-recommended lymph node evaluation (Table 13). In this period, higher volume hospitals and those with ACOSOG affiliation were more likely to have an initial median lymph node count ≥12 (Table 13). However, guideline recommended lymph node evaluation did not vary by teaching hospital status, hospital ownership, hospital volume, location, or NCI Cancer center status.

Short-term Maintenance or Improvement (1999-2001)

Of the 228 hospitals included in our study, 28.1% (n=64/228) improved to or maintained guideline-recommended lymph node evaluation in the short-term. Of these 64 hospitals, 51.7% (n=31/60) of those performing guideline-recommended evaluation in the initial study period maintained guideline-recommended care, while 19.6% (n=33/168) of those performing below guidelines improved in the short-term (Figure 6). Multivariate analyses demonstrated that, after adjusting for patient case-mix, prior hospital guideline performance (OR (95% CI): 4.02 (1.92, 8.41)) and ACOSOG membership (OR (95% CI): 3.39 (1.39, 8.30)), and urban location (OR (95% CI): 2.66 (1.12, 6.31)) were significantly associated with short-term improvement or maintenance of guideline-recommended lymph node evaluation (Table 14).

Medium-term Maintenance or Improvement (2002-2004)

By 2002-2004, 44.7% (n=102/228) of hospitals had improved to or maintained guideline-recommended lymph node evaluation. Of these hospitals, 65.0% (n=39/60) of those performing guideline-recommended evaluation in the initial study period maintained guideline-recommended care, while 37.5% (n=63/168) of those performing below guidelines improved in the medium-term (Figure 6). Multivariate analyses demonstrated that, even in the medium-term, prior hospital

performance (OR (95% CI): 2.41 (1.17, 4.94)) and ACOSOG membership (OR (95% CI): 6.05 (2.32, 15.77)) remained significantly associated with improvement or maintenance of guideline-recommended lymph node evaluation (Table14). However, urban location was no longer a significant predictor of medium-term improvement or maintenance of guideline-recommended lymph node evaluation (OR (95% CI): 1.52 (0.76, 3.01)).

Long-term Maintenance or Improvement (2005-2007)

By 2005-2007, 70.6% (n=161/228) of hospitals had improved to or maintained guideline-recommended lymph node evaluation. Of these hospitals, 80.0% (n=48/60) of those performing guideline-recommended evaluation in the initial study period maintained guideline-recommended care, while 67.3% (n=113/168) of those performing below guidelines improved in the long-term (Figure 6). However, after adjusting for patient case-mix, multivariate analyses identified no significant differences in improvement or maintenance of guideline-recommended lymph node evaluation across hospital characteristics (Table 14).

While NCI cancer center status and hospital bed size were available to include in our multivariate models, we found each variable to be highly correlated with ACOSOG membership and hospital volume respectively, which diminished the significance of both sets of variables when all were included in our models. We, therefore, chose to remove these characteristics from our final multivariate models.

Further, as the relationship between hospital characteristics and improvement or maintenance of guideline-recommended lymph node evaluation may change depending on how the characteristics or outcomes are defined, we performed several sensitivity analyses. First, we evaluated each of our multivariate models slightly varying the cut-point for guideline-recommended evaluation (at 11 [Appendix 24] and 13 [Appendix 25] nodes respectively). Second, we removed non-significant factors from our analysis to see if this changed the

relationship between hospital characteristics and our outcomes. Under all analyses, our conclusions remained unchanged.

Discussion

In this study of 228 hospitals surgically treating non-metastatic colon cancer patients in the SEER-Medicare database, we found that prior hospital performance and ACOSOG specialty membership were most strongly associated with short- and medium-term improvement or maintenance of guideline-recommended lymph node evaluation after the introduction of surgical practice guidelines; however, these factors were no longer associated with guideline-recommended lymph node evaluation in the long-term. Rather, by 2005-2007, more than half (70.6%, n=161) of all hospitals were performing at or above guideline-recommended care, which did not vary significantly across hospital characteristics. The results suggest that initially, rewarding hospitals for compliance with guidelines would primarily provide financial incentives to those who were already top performers while creating additional barriers to improvement among underperformers- as one of the factors most strongly associated with improvement or maintenance of guideline-recommended lymph node evaluation was guideline-recommended performance prior to guideline publication.

Our results are consistent with previous work on the topic of guideline adherence. In a 2011 study of colon cancer patients in the SEER-Medicare database, Nathan et al. examined patient and provider characteristics associated with guideline-level lymph node evaluation at any point in time.[81] They found that the most modifiable variation in lymph node evaluation occurred at the hospital level. Specifically, they identified NCI cancer center designation and teaching status as significantly associated with adequate evaluation. They note, however, that these factors may in fact be proxies for hospital-level quality control measures, suggesting that these hospitals may have an overall higher baseline level of quality that can be generalized across the institution. Another study by Bilimoria et al.[28] of surgically treated colon cancer patients in the National

Cancer database from 1996-2005 additionally found that NCI designated cancer centers, which may provide for more dedicated resources to track and focus on quality improvement efforts in this area, were more likely to comply with the 12 lymph node guideline. Our study builds upon these findings, indicating that in addition to specialized hospitals (e.g., ACOSOG affiliated hospitals) the factor most strongly associated with improvement or maintenance of guideline-recommended lymph node evaluation over time was a hospital's prior performance.

Our study also builds upon previous studies examining the implications of setting quality guidelines or pay-for-performance standards based on standard criteria across all providers. In a previous study of thirty-one separate pay for performance initiatives covering more than twenty million enrollees, Rosenthal et al.[81] indicated that almost all of these programs created explicit winners and losers which would likely result in the redistribution of reimbursement from "low quality" to "high quality" providers. Further, the study noted that while some "low quality" providers may be sufficiently motivated to make investments necessary to acquire financial incentives, many may find that the costs would exceed the modest financial benefits of doing so. Finally, despite good intentions, there are also concerns that implementing pay-for-performance programs may lead to patient selection against sicker or non-compliant patients. Another study by Rosenthal et al.[80] examined the effectiveness of pay for performance initiatives in a large health plan using administrative reports of physician group quality.[82] Using three process measures of clinical quality including cervical cancer screening, mammography and hemoglobin A testing, they found that for all measures, physician groups with baseline performance at or above the performance threshold for receipt of a bonus improved the least but garnered the largest share of the bonus payments. They concluded that paying clinicians to reach a common, fixed performance target may produce little gain in quality for the resources expended and primarily reward those with high baseline performance. Finally, Mehrotra et al.[83] conducted a study of 79 physician groups in Massachusetts finding that practices with a pay for performance initiative

were more likely to have undertaken a quality improvement program to improve on that measure.[83] However, the incentive and its associated improvement were modest at best. Further, physician group leaders said that incentives of five percent or more of revenue would be necessary to increase emphasis on specific quality improvement endeavors. As a result, the potential for undertaking quality improvement programs would be greater for large groups and integrated delivery systems that had more resources to support these efforts -- again biasing the receipt of financial incentives towards those traditionally performing well on quality indicators. Consistent with each of these findings, our study indicates that rewarding compliance with these surgical guidelines through financial incentives would primarily reward high achievers. Further, it would give the most money to those already performing well at the start, creating an environment of limited incentive for those performing in the bottom quartiles to improve. These findings are important in the context of future pay-for-performance initiatives and policy debates.

While our study provides important implications for quality improvement initiatives, we acknowledge several data-related limitations. First, this study focused solely on patients 66 years and older residing in SEER areas. However, the majority of colon cancer cases are diagnosed in individuals 65 years and older and SEER now represents over 26% of the US population. Additionally, we were unable to determine if hospital-level node removal performance would vary if we were to include all patients undergoing colon cancer resection at the institution. It is unlikely that these estimates would vary greatly if these individuals were included, however, due to the small proportion of cases in this additional population.

Overall, our study provides important insights into the potential implications for future pay for performance initiatives in surgical oncology practice. Policy makers should consider programs aimed to improve performance of “low quality” performers rather than incentivize the status quo already provided by “high quality” institutions, as the institutions performing guideline-recommended lymph node evaluation prior to guideline publication were the same

hospitals most likely to remain adherent in each subsequent time period. Additionally, researchers should focus on identifying the most important indicators of quality care that most influence mortality and comorbidity within this population. Learning from the evolution of quality improvement efforts over time will provide policy-makers, administrators and payers with information to guide future resource planning and areas to focus future quality improvement efforts.

**Table 12: Patient Characteristics by Year of Diagnosis %(N)**

| Patient Characteristics (N=24,926) | | | | | |
|---|---|---|---|---|---|
| **Year of Diagnosis** | **1996-1998** | **1999-2001** | **2002-2004** | **2005-2007** | **P-Value** |
| **Number of Patients** | 5,199 | 5,406 | 7,700 | 6,621 | |
| **Age** 66-69 | 13.5 (703) | 13.3 (717) | 13.7 (1,057) | 14.5 (959) | <0.001 |
| 70-74 | 23.5 (1,220) | 20.6 (1,114) | 20.5 (1,579) | 19.8 (1,313) | |
| 75-79 | 24.6 (1,279) | 24.9 (1,346) | 24.6 (1,896) | 22.6 (1,498) | |
| 80-84 | 20.1 (1,046) | 21.1 (1,143) | 22.5 (1,728) | 22.6 (1,497) | |
| ≥85 | 18.3 (951) | 20.1 (1,086) | 18.7 (1,440) | 20.5 (1,354) | |
| **Race** | | | | | <0.001 |
| White | 89.1 (4,632) | 87.9 (4,754) | 85.6 (6,590) | 84.6 (5,599) | |
| Black | 5.4 (283) | 5.5 (295) | 6.6 (508) | 6.6 (439) | |
| Other/Unknown | 5.5 (284) | 6.6 (357) | 7.8 (602) | 8.8 (583) | |
| **Sex** | | | | | 0.26 |
| Female | 58.8 (3,059) | 59.5 (3,216) | 57.8 (4,450) | 58.7 (3,883) | |
| Male | 41.2 (2,140) | 40.5 (2,190) | 42.2 (3,250) | 41.4 (2,738) | |
| **Charlson Comorbidity Score** | | | | | <0.001 |
| 0 | 65.0 (3,379) | 63.2 (3,418) | 60.0 (4,623) | 58.1 (3,845) | |
| 1 | 17.2 (896) | 16.7 (902) | 17.6 (1,354) | 17.0 (1,130) | |
| 2 | 8.7 (452) | 9.7 (525) | 10.7 (824) | 11.4 (753) | |
| ≥3 | 9.1 (472) | 10.4 (561) | 11.7 (899) | 13.5 (893) | |
| **AJCC Stage** | | | | | <0.001 |
| I | 23.5 (1,223) | 27.2 (1,468) | 27.9 (2,144) | 26.9 (1,781) | |
| II | 44.6 (2,319) | 42.2 (2,284) | 40.5 (3,120) | 41.0 (2,712) | |
| III | 31.9 (1,657) | 30.6 (1,654) | 31.6 (2,436) | 32.1 (2,128) | |
| **Tumor Location** | | | | | <0.001 |
| Proximal Colon | 67.9 (3,532) | 71.2 (3,847) | 71.3 (5,488) | 72.6 (4,806) | |
| Distal Colon | 32.1 (1,667) | 28.8 (1,559) | 28.7 (2,212) | 27.4 (1,815) | |
| **Grade** | | | | | 0.33 |
| Well/Moderately Differentiated | 76.1 (3,958) | 74.9(4,052) | 76.1 (5,858) | 75.2 (4,981) | |
| Poorly/Undifferentiated | 23.9 (1,241) | 25.1 (1,354) | 23.9 (1,842) | 24.8 (1,640) | |
| **Lymph Node Evaluation** | | | | | |
| ≥12 Nodes | 41.2 (2,141) | 43.2 (2,336) | 51.7 (3,979) | 65.1 (4,312) | <0.001 |

**Table 13: Hospital Characteristics in the Initial Study Period (1996-1998), N (%)**

| | All Hospitals | Hospitals with Median LN count ≥12 | Hospitals with Median LN count <12 | P-Value |
|---|---|---|---|---|
| **Total Number of Hospitals** | 228 | 60 | 168 | |
| **Organizational Characteristics** | | | | |
| **Teaching Hospital** No | 108 (47.4) | 26 (43.3) | 79 (47.0) | 0.62 |
| Yes | 120 (52.6) | 34 (56.7) | 89 (53.0) | |
| **Hospital Ownership** | | | | 0.67 |
| Non-Profit | 161 (70.6) | 45 (75.0) | 116 (69.0) | |
| For-Profit | 25 (11.0) | 6 (10) | 19 (11.3) | |
| Government | 42 (18.4) | 9 (15.0) | 33 (19.7) | |
| **Number of Hospital Beds** | | | | 0.02 |
| <200 | 83 (36.4) | 20 (33.3) | 20 (37.5) | |
| 200-299 | 67 (29.4) | 12 (20) | 55 (32.7) | |
| 300-399 | 33 (14.5 | 8 (13.4) | 25 (14.9) | |
| ≥400 | 45 (19.7) | 20 (33.3) | 25 (14.9) | |
| **Hospital Volume 1996-1998, in Quartiles** | | | | 0.19 |
| 1 (6-13 procedures) | 60 (26.3) | 14 (23.3) | 46 (27.4) | |
| 2 ( 14-21 procedures) | 55 (24.1) | 13 (21.7) | 42 (25.0) | |
| 3 (22-37 procedures) | 60 (26.3) | 12 (21.7) | 47 (28.0) | |
| 4 (≥38 procedures) | 53 (23.3) | 20 (33.3) | 33 (19.6) | |
| **Hospital Location** | | | | 0.49 |
| Rural | 49 (21.5) | 11 (18.3) | 38 (22.6) | |
| Urban | 179 (78.5) | 49 (81.7) | 130 (77.4) | |
| **ACOSOG Member (Assessed in 2002)** | | | | 0.03 |
| No | 188 (82.5) | 44 (73.3) | 144 (85.7) | |
| Yes | 40 (17.5) | 16 (26.7) | 24 (14.3) | |
| **NCI Sponsored Cancer Center (in 2002)** | | | | 0.77 |
| No | 219 (96.1) | 58 (96.7 ) | 161 (95.8) | |
| Yes | 9 (3.9) | 2 (3.3) | 7 (4.2) | |

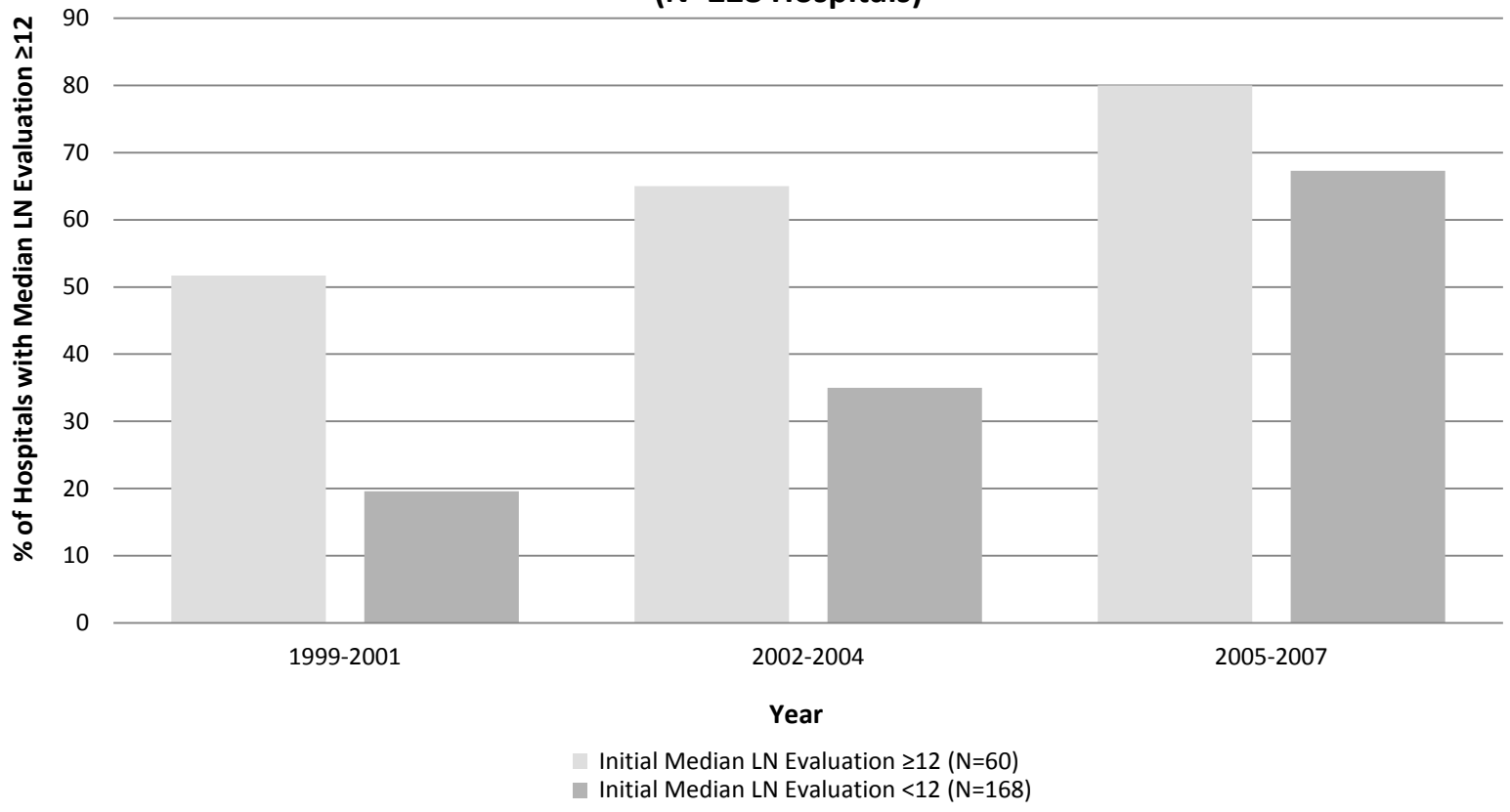
**Table 14: Hospital Factors associated with Improvement or Maintenance of Adequate Lymph Node Evaluation (i.e. Median LN Evaluation ≥12), Odds Ratios (95% CI)***

| | Short-Term (1999-2001) | | Medium-Term (2002-2004) | | Long-Term (2005-2007) | |
|---|---|---|---|---|---|---|
| **Initial Median LN Evaluation ≥12 (1996-1998)** | | | | | | |
| | Ref. | | Ref. | | Ref. | |
| **Yes** | 4.021 | (1.920, 8.419)* | 2.406 | (1.172, 4.943)* | 1.547 | (0.721, 3.317) |
| **Teaching Hospital** | | | | | | |
| No | Ref. | | Ref. | | Ref. | |
| Yes | 2.329 | (1.027, 5.282)* | 1.521 | (0.767, 3.014) | 1.604 | (0.817, 3.150) |
| **Hospital Ownership** | | | | | | |
| Non-Profit | Ref. | | Ref. | | Ref. | |
| For-Profit | 0.987 | (0.305, 3.187) | 0.487 | (0.167, 1.417) | 0.967 | (0.347, 2.694) |
| Government | 0.890 | (0.311, 2.542) | 1.954 | (0.791, 4.829) | 0.979 | (0.420, 2.281) |
| **Hospital Volume 1996-1998 (Quartiles)** | | | | | | |
| 1 (6-13 procedures) | Ref. | | Ref. | | Ref. | |
| 2 ( 14-21 procedures) | 1.316 | (0.463, 3.741) | 2.404 | (0.953, 6.063) | 2.446 | (1.026, 5.829) |
| 3 (22-37 procedures) | 1.012 | (0.353, 2.902) | 2.151 | (0.845, 5.475) | 1.251 | (0.536, 2.921) |
| 4 (≥38 procedures) | 1.762 | (0.576, 5.391) | 1.261 | (0.449, 3.542) | 2.553 | (0.892, 7.311) |
| **Hospital Location** | | | | | | |
| Rural | Ref. | | Ref. | | Ref. | |
| Urban | 1.293 | (0.478, 3.496) | 2.659 | (1.122, 6.305) | 1.406 | (0.638, 3.098) |
| **ACOSOG Member (Assessed in 2002)** | | | | | | |
| No | Ref. | | Ref. | | Ref. | |
| Yes | 3.393 | (1.386, 8.308)* | 6.048 | (2.320, 15.766)* | 2.496 | (0.840, 7.414) |
| **C-Statistic** | 0.81 | | 0.78 | | 0.72 | |

*Also Adjusted for Hospital-Level patient factors including: % of patients ≥80 years of age, % non-white patients, % of male patients, % of proximal tumors, % of high grade tumors, % of patients with a high Charlson score (≥3), % high staged (AJCC Stage III) cancers treated by the hospital.

| | | | |
|---|---|---|---|
| **Number of Patients** | 10,605 | 12,899 | 11,820 |
| **Number of Hospitals** | 228 | 228 | 228 |

**Figure 6: Hospital-Level Guideline-Recommended Lymph Node (LN) Evaluation over Time , by Level of Initial Evaluation (N=228 Hospitals)**



## Conclusions and Future Implications

This 3-paper exam further examined the relationship between lymph node evaluation and improved survival for colon cancer. Colon cancer care provides an important opportunity to identify how providers and policymakers can achieve high quality outcomes in the context of quality guidelines. Previous studies have identified that among patients surgically treated for colon cancer, better survival has been demonstrated in those with more lymph nodes evaluated. Evaluated at the time of surgery, lymph node involvement (i.e. node positive disease) indicates advanced disease among colon cancer patients and a recommendation for adjuvant chemotherapy. Over the past 20 years, several practice organizations and consensus panels have identified the surgical evaluation of 12 or more lymph nodes as an important quality indicator for appropriate staging and treatment of newly diagnosed colon cancer patients. However, the exact mechanism behind more extensive lymph node evaluation and improved survival remains contentious. Using the Surveillance, Epidemiology and End Results (SEER) data and the SEER-Medicare data, which combines a set of cancer registry data linked to Medicare administrative claims, this research evaluated current gaps in knowledge surrounding the achievement and impact of lymph node quality guidelines for colon cancer care by l) further evaluating the mechanism between lymph node evaluation and survival 2) identifying whether high quality comprehensive care might account for this relationship and 3) understanding how to significantly improve guideline adherence among providers of colon cancer care. Overall, this research provides timely and significant evidence for future guideline recommendations surrounding the relative impact of lymph node evaluation for colon cancer care.

### *Mechanisms of and Justification for Quality Guidelines*

Chapter 3 of this dissertation calls into question the presumed mechanism between higher lymph node evaluation and improved survival. Specifically, the results demonstrate that although lymph node evaluation has increased dramatically over the past 20 years, there has been no

subsequent increase in the number of lymph node positive cancers in the population. Further, although patients with a larger number of lymph nodes evaluated are only slightly more likely to be node-positive, these patients have significantly better survival than those with fewer nodes evaluated. This improved survival relationship among those with more lymph nodes evaluated was seen in patients with both node positive and node negative disease. Combined, these findings suggest that upstaging cannot be the mechanism underlying the relationship between increase lymph node evaluation and improved colon cancer survival.

Overall, these findings may bring scrutiny to similar guidelines in other cancers. Future studies should continue to evaluate the presumed mechanism behind lymph node evaluation and improved outcomes in other cancers as well as the relationships between guideline adherence and improved outcomes more broadly. Such studies might evaluate the relationship between these guidelines, the types of individuals who adopt them and their resulting outcomes as a means to further identify why guidelines may lead to improved outcomes. Other avenues for research might further examine the biologic mechanisms between lymph node evaluation and improved survival in order to identify the molecular impact of lymph node removal on outcomes after cancer surgery. As healthcare resources are continually constrained and efforts emerge to promote efficient and effective means for healthcare utilization, these studies will become crucial for identifying guidelines that will likely have the largest impact on improved outcomes and promote use of targeted, effective healthcare utilization in the population.

***Quality of Care along the Cancer Continuum***

Chapter 4 further evaluates the mechanism between more extensive lymph node evaluation and improved survival by examining whether this relationship could be partially explained by more comprehensive post-surgical care. This second study demonstrates that among surgically treated AJCC stage III colon cancer patients in the SEER-Medicare linked data, individuals with adequate lymph node evaluation were no more likely to receive comprehensive

post-surgical care than those with <12 nodes evaluated. Further, while adequate lymph node evaluation for colon cancer was associated with lower mortality at diagnosis, after patients survived 3 years, the association between lymph node evaluation and lower hazard of death was no longer significant. However, post-surgical care remained strongly associated with lower long-term mortality, indicating that post-surgical care may partially explain the relationship between lymph node evaluation and mortality.

These findings present two key areas for future research. First, these findings suggest that receiving high quality surgical care does not necessarily lead to patients receiving more comprehensive follow-up care after this initial treatment. At the same time, receiving comprehensive post-surgical care was strongly associated with long-term survival, indicating that future efforts should focus on improving adherence to recommended surveillance and treatment after a patient is diagnosed. While many factors including patient preferences, insurance and knowledge about the most effective treatments can influence who ultimately receives post-surgical care, identifying the reasons behind non-adherence will be important for designing effective survivorship programs for patients. Second, these findings bring further scrutiny to the proposed mechanism behind more extensive lymph node evaluation and improved survival, suggesting that receipt of post-surgical care after colon cancer surgery may partially explain this relationship. This relationship should be examined in other cancers, particularly those with high survivorship rates and a large post-treatment surveillance component after treatment. Understanding how to identify those patients who are less likely to receive high-quality care across the cancer continuum will be important for creating survivorship programs that target individuals less likely to complete recommended adjuvant therapies or undergo post-treatment surveillance.

***Adoption of Guidelines***

Finally, Chapter 5 examined hospital-level factors that were associated with institutional improvement or maintenance of adequate lymph node evaluation after the introduction of surgical quality guidelines for colon cancer. The results showed that between 1996-2007, there were significant improvements in hospital performance for guideline-recommended lymph node evaluation. After adjusting for a hospital's case-mix of colon cancer patients, a hospital's prior guideline performance, teaching status and American College of Surgeon's Oncology Group membership were all significantly associated with short and medium-term improvement or maintenance of guideline-recommended lymph node evaluation; however, these factors were not associated with long-term performance. The results suggest that initially, rewarding hospitals for compliance with guidelines would primarily provide financial incentives to those who were already top performers while creating additional barriers to improvement among underperformers.

Overall, this research provides important insights into the potential implications for future pay-for-performance initiatives in surgical oncology practice, regardless of the utility of this particular guideline for lymph node evaluation. Policy makers should consider programs aimed to improve performance of "low quality" performers rather than incentivize the status quo already provided by "high quality" institutions. Additionally, researchers should focus on identifying the most important indicators of quality care that most influence mortality and comorbidity within this population. Learning from the evolution of quality improvement efforts over time will provide policy-makers, administrators and payers with information to guide future resource planning and areas to focus future quality improvement efforts.

In conclusion, understanding the mechanism that influences the node-survival relationship and leads to improved adherence to guideline recommended care will be instrumental in the design of future quality improvement programs. While lymph node evaluation alone may

not drive improved survival, understanding the best combined mechanisms for influencing guideline recommended care will be important for identifying those components that significantly improve the quality of cancer care in the US.

**Bibliography**


1. National Cancer Institute: General information about colorectal cancer. 2010.

2. Altekruse SF, Kosary CL, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2007. Bethesda, MD: National Cancer Institute; 2010.

3. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol 2003;21:2912-9.

4. Bui L, Rempel E, Reeson D, et al. Lymph node counts, rates of positive lymph nodes, and patient survival for colon cancer surgery in Ontario, Canada: a population-based study. J Surg Oncol 2006;93:439-45.

5. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: A population-based study. Ann Surg 2006;244:602-10.

6. Chang GJ, Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 2007;99:433-41.

7. Swanson RS, Compton CD, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 2003;10:65-71.

8. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual: Springer; 2009.

9. Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. J Clin Oncol 1993;11:1879-87.

10. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. NEJM 1990;322:352-8.

11. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for Colon and Rectal Cancer Surgery. J Natl Cancer Inst 2001;93:583-96.

12. Otchy D, Hyman NH, Simmang C, et al. Practice parameters for colon cancer. Dis Colon Rectum 2004;47:1269-84.

13. ASCO/NCCN Quality Measures: Breast and Colorectal Cancers. 2007. (Accessed Feb 22, 2011, at http://www.asco.org/ASCO/Downloads/Cancer%20Policy%20and%20Clinical%20Affairs/NCCN/ASCO%20NCCN%20Quality%20Measures%20table%20web%20posting%20with%20CoC%200507.pdf.)

14. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic Factors in Colorectal Cancer. College of American Pathologists Consensus Statement. Arch Pathol Lab Med 2000;124:979-94.

15. Simunovic M, Baxter NN. Lymph node counts in colon cancer surgery: lessons for users of quality indicators. JAMA 2007;298:2194-5.

16. Wong SL, Ji H, Hollenbeck BK, et al. Hospital and lymph node examination rates and survival after resection for colon cancer. JAMA 2007;298:2149-54.

17. Baxter NN, Ricciardi R, Simunovic M, et al. An evaluation of the relationship between lymph node number and staging in pT3 colon cancer using population-based data. Dis Colon Rectum 2010;53:65-70.

18. Johnson PM, Porter GA, Ricciardi R, et al. Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer. J Clin Oncol 2006;24:3570-5.

19. Baxter NN, Virnig DJ, Rothenberger DA, et al. Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 2005;97:219-25.

20. Wang J, Kulaylat M, Rockette H, et al. Should total number of lymph nodes be used as a quality of care measure for stage III colon cancer? Ann Surg 2009;249:559-63.

21. Nathan H, Shore A, Anders RA, et al. Variation in lymph node assessment after colon cancer resection: patient, surgeon, pathologist, or hospital? J Gastrointest Surg 2010;15:471-9.

22. Baxter NA. Is lymph node count an ideal quality indicator for cancer care? J Surg Oncol 2009;99:265-8.

23. Performance Measurement: Accelerating Improvement. Washington DC: National Academies Press; 2006.

24. Malin JL, Schneider EC, Schneider AM, et al. Results of the National Initiative for Cancer Care Quality: How Can We Improve the Quality of Cancer Care in the United States? JCO 2006;24:626-34.

25. Hampton T. Cancer Care Quality Assessed. JAMA 2006;295:1238.

26. National Comprehensive Cancer Network: Clinical practice guidelines in oncology: colon cancer, version 2. 2006.

27. National Cancer Institute: Cancer Trends Progress Report 2009/2010 Update. 2010.

28. Bilimoria KY, Stewart AK, Edge SB. Lymph node evaluation as a colon cancer quality measure: A national hospital report card. J Natl Cancer Inst 2008;100:1310-7.

29. Prandi M, Lionetto R, Bini A, et al. Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy: results of a secondary analysis of a large scale adjuvant trial. Ann Surg 2002;235:458-63.

30. Carloss H, Huang B, Cohen A, Carloss E, Wyatt S, Tucker T. The impact of number of lymph nodes removed on 5-year survival in stage II colon and rectal cancer. J Ky Med Assoc 2006;102:345-7.

31. Cserni G, Vinh-Hung V, Burzykowski T. Is there a minimum number of lymph nodes that should be histologically assessed for a reliable nodal staging of T3N0M0 colorectal carcinomas? J Surg Oncol 2002;81:63-9.

32. Jestin P, Pahlman L, Glimelius B, Gunnarsson U. Cancer staging and survival in colon cancer is dependent on the quality of the pathologists' specimen examination. Eur J Cancer 2005;41:2071-78.

33. Goldstein NS. Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years: recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. Am J Surg Pathol 2002;26.

34. Sarli L, Bader G, Iusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. Eur J Cancer 2005;41:272-9.

35. Caplin S, Cerottini JP, Bosman FT, et al. For patients with Dukes' B (TNM stage II) colorectal carcinoma, examination of 6 or fewer lymph nodes is related to poor prognosis. Cancer 1998;83.

36. Cianchi F, Palomba A, Boddi V, et al. Lymph node recovery from colorectal tumor specimens: recommendation for a minimum number of lymph nodes to be examined. World J Surg 2002;26:384-9.

37. Gumus M, Yumuk PF, Atalay G, et al. What is the optimal number of lymph nodes to be dissected in colorectal cancer surgery? Tumori 2005;91.

38. Law CH, Wright FC, Rapanos T, et al. Impact of lymph node retrieval and pathological ultra-staging on the prognosis of stage II colon cancer. J Surg Oncol 2003;84.

39. Ratto C, Sofo L, Ippoliti M, et al. Accurate lymph-node detection in colorectal specimens resected for cancer is of prognostic significance. Dis Colon Rectum 1999;42.

40. Wong JH, Bowles BJ, Bueno R, et al. Impact of the number of negative nodes on disease-free survival in colorectal cancer patients. Dist Colon Rectum 2002;45:1341-8.

41. Yoshimatsu K, Ishibashi K, Umehara A, et al. How many lymph nodes should be examined in Dukes' B colorectal cancer? Determination on the basis of cumulative survival rate. Hepatogastroenterology 2005;15:1703-6.

42. Fleming ID, Cooper, J.S., Henson, D.E., et al., ed. AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott; 1997.

43. Desch CE, Benson AB, Somerfield MR, et al. Colorectal Cancer Surveillance: 2005 Update of an American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23:8512-9.

44. Desch CE, McNiff KK, Schneider EC, et al. American Society of Clinical Oncology/National Comprehensive Cancer Network Quality Measures. J Clin Oncol 2008;26:3631-7.

45. Rex DK, Kahi CJ, Levin B, et al. Guidelines for Colonoscopy Surveillance after Cancer Resection: A Consensus Update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. CA Cancer J Clin 2006;56:160-7.

46. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-update based on new evidence. Gastroenterology 2003;124:544-60.

47. Freiman MP. The rate of adoption of new procedures among physicians. The impact of specialty and practice characteristics. Med Care 1985;23:939-45.

48. Parsons HM, Tuttle TM, Kuntz KM, et al. Association between lymph node evaluation for colon cancer and node positivity over the past 20 years. JAMA 2011;306:1089-97.

49. Surveillance, Epidemiology and End Results (SEER) Program Research Data (1973-2007). 2010. (Accessed at www.seer.cancer.gov.)

50. Nattinger AB, McAuliffe TL, Schapira MM. Generalizability of the surveillance, epidemiology, and end results registry population: factors relevant to epidemiologic and health care research. J Clin Epidemiol 1997;50:939-45.

51. Baxter NN, Morris AM, Rothenberger DA, et al. Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. Int J Radiat Oncol Biol Phys 2005;61:426-31.

52. Understanding the changes from the sixth to the seventh edition of the AJCC cancer staging manual. 2010. (Accessed at http://www.cancerstaging.org/staging/changes2010.pdf.)

53. How is colorectal cancer staged? (Accessed August 5, 2011, at http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-staged.)

54. Okabe S, Shia J, Nash G, et al. Lymph node metastasis in T1 adenocarcinoma of the colon and rectum. Journal of Gastrointestinal Surgery 2004;8:1032-40.

55. Nivatvongs S, Rojanasakul A, Reiman H, et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. Diseases of the Colon & Rectum 1991;34:323-8.

56. Liefers G-J, Cleton-Jansen A-M, van de Velde CJH, et al. Micrometastases and Survival in Stage II Colorectal Cancer. New England Journal of Medicine 1998;339:223-8.

57. Ho SB, Hyslop A, Albrecht R, et al. Quantification of Colorectal Cancer Micrometastases in Lymph Nodes by Nested and Real-Time Reverse Transcriptase-PCR Analysis for Carcinoembryonic Antigen. Clinical Cancer Research 2004;10:5777-84.

58. Bernini A, Spencer M, Frizelle S, et al. Evidence for colorectal cancer micrometastases using reverse transcriptase-polymerase chain reaction analysis of MUC2 in lymph nodes. Cancer Detect Prev 2000;24:72-9.

59. Gross CP, Andersen MS, Krumholz HM, McAvay GJ, Proctor D, Tinetti ME. Relation Between Medicare Screening Reimbursement and Stage at Diagnosis for Older Patients With Colon Cancer. JAMA: The Journal of the American Medical Association 2006;296:2815-22.

60. Meissner HI, Breen N, Klabunde CN, et al. Patterns of Colorectal Cancer Screening Uptake among Men and Women in the United States. Cancer Epidemiology Biomarkers & Prevention 2006;15:389-94.

61. SEER-Medicare Linked Database. 2010. (Accessed Web Page, 2010, at http://healthservices.cancer.gov/seermedicare/.)

62. Surveillance, Epidemiology and End Results (SEER) Program Research Data (1973-2007). 2010. (Accessed at www.seer.cancer.gov.)

63. Stephen AE, Berger DL. Shortened length of stay and hospital cost reduction with implementation of an accelerated clinical care pathway after elective colon resection. Surgery 2003;133:277-82.

64. Warren JL, Klabunde CN, Schrag D, et al. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Medical Care 2002;40:IV-3-IV-18.

65. Cooper G, Virnig B, Klabunde C, et al. Use of SEER-Medicare Data for Measuring Cancer Surgery. Medical Care 2002;40:IV-43.

66. Warren JL, Harlan LC, Fahey A, et al. Utility of the SEER-Medicare data to identify chemotherapy use. Medical Care 2002;40:IV-55-IV-61.

67. Klabunde C, Warren J, Legler JM. Assessing comorbidity using claims data. Med Care 2002;40:IV-26-35.

68. Charlson ME, Pompei P, Alex KL, et al. A new method of classifying comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373-83.

69. Freedman RA, Virgo KS, He Y, et al. The association of race/ethnicity, insurance status, and socioeconomic factors with breast cancer care. Cancer 2011;117:180-9.

70. Katz ML, Donohue KA, Alfano CM, Day JM, Herndon JE, Paskett ED. Cancer Surveillance behaviors and psychosocial factors among long-term survivors of breast cancer. Cancer and Leukemia Group B 79804. Cancer 2009;115:480-8.

71. Potosky AL, Harlan LC, Kaplan RS, et al. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. J Clin Oncol 2002;20:1192-202.

72. Earle CC, Neville BA. Under use of necessary care among cancer survivors. Cancer 2004;101:1712-9.

73. Elston Lafata J, Cole Johnson C, Ben-Menachem T, et al. Sociodemographic Differences in the Receipt of Colorectal Cancer Surveillance Care Following Treatment With Curative Intent. Medical Care 2001;39:361-72.

74. Parsons HM, Habermann EB, Tuttle TM, et al.. Conditional survival of extremity soft-tissue sarcoma: results beyond the staging system. Cancer 2011;117:1055-60.

75. Kato I, Severson RK, Schwartz AG. Conditional median survival of patients with advanced carcinoma: surveillance, epidemiology and end results data. Cancer 2001;92:2211-9.

76. Christensen LH, Engholm G, Ceberg J, et al. Can the survival difference between breast cancer patients in Denmark and Sweden in 1989 and 1994 be explained by patho-anatomical variables? A population-based study. Eur J Cancer 2004;40:1233-43.

77. Meng L, Maskarinec G, Lee J. Ethnicity and conditional breast cancer survival in Hawaii. J Clin Epidemiol 1997;50:1289-96.

78. Merrill RM, Henson DE, Ries LA. Conditional survival estimates in 34,963 patients with invasive carcinoma of the colon. Dis Colon Rectum 1998;41:1097-106.

79. Health Care Financing Organization. Medicare coverage of colorectal cancer screening. Program memoranda to intermediaries/carriers. Baltimore; 1997.

80. Rosenthal MB, Frank RG, Li Z, et al. Early experience with pay-for-performance: from concept to practice. JAMA 2005;294:1788-93.

81. Rosenthal MB, Fernandopulle R, Song HR, et al. Paying for quality: providers incentives for quality improvement. Health Affairs 2004;23:127.

82. Rosenthal MB, Frank RG, Epstein AM. Early experience with pay for performance: from concept to practice. JAMA 2005;294:1788-93.

83. Mehrotra A, Pearson SD, Coltin KL, et al. The response of physician groups to p4p initiatives. American Journal of Managed Care 2007;13:249-55.

84. Hosmer D, Lemeshow S. Applied Logistic Regression: John Wiley and Sons, Inc.; 1989.

# Appendices

**Appendix 1: Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Logistic Regression Model Evaluating the Association between Lymph Node Evaluation and Relative Odds of Node Positivity**

The following sensitivity analyses evaluate the presence of a significant interaction between the level of lymph node evaluation a patient receives and other characteristics of those patients. Specifically, we assessed whether a significant interaction was present between the level of lymph node evaluation and patient age, race, sex, t-stage, and tumor grade. A significant interaction would indicate that the association between lymph node evaluation and odds of node-positivity varied by one or multiple of these patient characteristics. We used the likelihood ratio test to evaluate the presence of a significant interaction in our models.[84] The likelihood ratio test uses the ratio of the maximized value of the likelihood function for the interaction model (L1) over the maximized value of the likelihood function for the full model (L0). The likelihood test statistic equals:

$$-2\log\left(\frac{L_0}{L_1}\right) = -2[\log(L_0) - \log(L_1)] = -2(L_0 - L_1)$$

This log transformation of the likelihood function yields a chi-square statistic. We considered a p-value for this chi-square statistic of <0.05 to be significant.

For all interaction analyses, the Full model indicates a logistic regression model evaluating the association between lymph node evaluation and relative odds of node positivity, adjusting for patient age, race, sex, AJCC stage, tumor grade, tumor location, type of surgical resection, year of diagnosis and registry.

LN Evaluation*Age Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 98773.27 | 24 | 0.05 |
| Full Model + Interaction term between LN Evaluation*age (L1) | 98736.03 | | |
| Difference | 37.24 | | |

LN Evaluation*Race Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 98773.27 | 12 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Race (L1) | 98764.88 | | |
| Difference | 8.39 | | |

**Appendix 1 (Continued): Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Logistic Regression Model Evaluating the Association between Lymph Node Evaluation and Relative Odds of Node Positivity**

LN Evaluation*Sex Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 98773.27 | 6 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Sex (L1) | 98769.12 | | |
| Difference | 4.15 | | |

LN Evaluation*T-stage Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 98773.27 | 6 | 0.05 |
| Full Model + Interaction term between LN Evaluation*T-stage (L1) | 98769.12 | | |
| Difference | 4.15 | | |

LN Evaluation*Tumor Grade Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 98773.27 | 12 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Tumor Grade (L1) | 98764.34 | | |
| Difference | 8.93 | | |

The interaction terms for LN Evaluation and race, sex and tumor grade were all non-significant. While the interaction terms for age*LN Evaluation and T-Stage*LN Evaluation were borderline significant, when stratified by these factors our conclusions about the association between more extensive lymph node evaluation and odds of node-positivity as well as survival remain unchanged (See appendices 2 and 3).

**Appendix 2: Relative Odds of Node Positivity among those with at Least One Lymph Node Evaluated, Multivariate Logistic Regression Stratified by T-Stage (N=83,671)**

| | Odds Ratios [95% Confidence Interval] | | | |
|---|---|---|---|---|
| | T-Stage I N=8,788 | T-Stage II N=10,519 | T-Stage III N=44,380 | T-Stage IV N=19,984 |
| **Lymph Nodes Evaluated** | | | | |
| **1-8** | Ref | Ref | Ref | Ref |
| **9-11** | 1.13 [0.89, 1.42] | **1.29 [1.12, 1.50]** | **1.28 [1.20, 1.36]** | **1.30 [1.19, 1.42]** |
| **12-15** | **1.29 [1.02, 1.64]** | **1.19 [1.02, 1.39]** | **1.28 [1.21, 1.36]** | **1.36 [1.24, 1.48]** |
| **16-19** | **1.53 [1.18, 1.99]** | **1.08 [0.91, 1.29]** | **1.25 [1.17, 1.34]** | **1.39 [1.25, 1.55]** |
| **20-29** | **1.42 [1.08, 1.87]** | **1.18 [0.99, 1.40]** | **1.18 [1.10, 1.25]** | **1.19 [1.08, 1.33]** |
| **30-39** | **1.69 [1.06, 2.67]** | 1.06 [0.79, 1.43] | **1.11 [1.00, 1.23]** | 1.06 [0.89, 1.27] |
| **≥40** | **1.76 [1.01, 3.06]** | **1.71 [1.21, 2.40]** | 0.97 [0.85, 1.10] | 1.09 [0.87, 1.37] |
| **C-Index** | 0.66 | 0.62 | 0.61 | 0.63 |

* Also adjusted for age, race, sex, tumor grade, tumor location, type of surgical resection, year of diagnosis and registry.
Bold indicates $p<0.05$

In this sensitivity analysis, we find that the relative association between lymph node evaluation and odds of node positivity remains relatively stable when patients are stratified by T-stage. We continue to conclude that patients with more extensive lymph node evaluation are only slightly more likely to be node-positive than those with few nodes evaluated.

**Appendix 2 (Continued): Relative Odds of Node Positivity among those with at Least One Lymph Node Evaluated, Multivariate Logistic Regression Stratified by Age (N=83,671)**

| | Odds Ratios [95% Confidence Interval] | | | | |
|---|---|---|---|---|---|
| | Age <50<br>N=6,838 | Age 50-59<br>N=12,083 | Age 60-69<br>N=19,425 | Age 70-79<br>N=25,203 | Age ≥80<br>N=20,122 |
| **Lymph Nodes Evaluated** | | | | | |
| **1-8** | Ref | Ref | Ref | Ref | Ref |
| **9-11** | **1.41 [1.17, 1.69]** | **1.22 [1.08, 1.39]** | **1.33 [1.21, 1.46]** | **1.30 [1.20, 1.41]** | **1.22 [1.11, 1.34]** |
| **12-15** | **1.19 [1.01, 1.41]** | **1.26 [1.12, 1.43]** | **1.27 [1.16, 1.40]** | **1.37 [1.26, 1.49]** | **1.25 [1.15, 1.37]** |
| **16-19** | **1.30 [1.08, 1.57]** | 1.12 [0.98, 1.28] | **1.17 [1.05, 1.30]** | **1.42 [1.29, 1.56]** | **1.32 [1.18, 1.46]** |
| **20-29** | **1.20 [1.01, 1.43]** | 1.05 [0.93, 1.20] | **1.22 [1.10, 1.36]** | **1.15 [1.04, 1.26]** | **1.30 [1.17, 1.44]** |
| **30-39** | 1.06 [0.85, 1.33] | 1.10 [0.90, 1.33] | 1.03 [0.87, 1.22] | 1.14 [0.98, 1.34] | 1.21 [0.99, 1.48] |
| **≥40** | 1.01 [0.78, 1.30] | 0.82 [0.64, 1.06] | 1.10 [0.88, 1.38] | 1.25 [0.99, 1.55] | 1.21 [0.91, 1.59] |
| **C-Index** | 0.73 | 0.74 | 0.74 | 0.73 | 0.72 |

* Also adjusted for age, race, sex, tumor grade, tumor location, type of surgical resection, year of diagnosis and registry. Bold indicates $p<0.05$

In this sensitivity analysis, we find that the relative association between lymph node evaluation and odds of node positivity remains relatively stable when patients are stratified by age. We continue to conclude that patients with more extensive lymph node evaluation are only slightly more likely to be node-positive than those with few nodes evaluated for most patients- if at all. In the youngest patients, the relationship is not statistically significant, indicating that in younger patients, higher lymph node evaluation is not associated with statistically significant increases in the relative odds of node positivity.

**Appendix 3: Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models, Stratified by T-Stage (N=86,394)**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death | | | |
|---|---|---|---|---|
| | T-Stage I N=8,788 | T-Stage II N=10,519 | T-Stage III N=44,380 | T-Stage IV N=19,984 |
| **Lymph Nodes Evaluated** | | | | |
| **0** | **1.26 [1.08, 1.49]** | **1.26 [1.01, 1.58]** | **1.31 [1.16, 1.49]** | **1.22[1.13, 1.31]** |
| **1-8** | Ref | Ref | Ref | Ref |
| **9-11** | 1.07 [0.92, 1.26] | **0.88 [0.78, 0.98]** | **0.83 [0.79, 0.87]** | **0.88 [0.84, 0.92]** |
| **12-15** | 0.94 [0.79, 1.12] | **0.93 [0.82, 1.04]** | **0.80 [0.76, 0.83]** | **0.81 [0.77, 0.84]** |
| **16-19** | 0.86 [0.68, 1.07] | **0.76 [0.65, 0.88]** | **0.71 [0.68, 0.75]** | **0.74 [0.70, 0.78]** |
| **20-29** | 0.98 [0.79, 1.21] | **0.78 [0.67, 0.91]** | **0.68 [0.65, 0.72]** | **0.75 [0.70, 0.79]** |
| **30-39** | 0.74 [0.44, 1.25] | **0.73 [0.54, 0.98]** | **0.63 [0.57, 0.69]** | **0.68 [0.61, 0.76]** |
| **≥40** | 0.84 [0.48, 1.47] | **0.56 [0.37, 0.84]** | **0.61 [0.53, 0.70]** | **0.63 [0.55, 0.72]** |

* Also adjusted for age, race, sex, tumor grade, tumor location, AJCC Stage, type of surgical resection, post-operative radiation, year of diagnosis and registry. Bold indicates $p<0.05$.

In this sensitivity analysis, we find that the relative association between lymph node evaluation and 5-year relative hazard of death remains relatively stable when patients are stratified by T-stage when compared to the findings in Tables 6a and 6b. We continue to conclude that patients with more extensive lymph node evaluation have a significantly lower 5-year relative hazard of death compared with those who have few nodes evaluated- with the exception of patient with T-1 disease who have no relative improvement in survival when more lymph nodes are evaluated.

**Appendix 3 (Continued): Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models, Stratified by Age (N=86,394)**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death | | | | |
|---|---|---|---|---|---|
| | Age <50 N=7,032 | Age 50-59 N=12,467 | Age 60-69 N=20,182 | Age 70-79 N=26,022 | Age ≥80 N=20,691 |
| **Lymph Nodes Evaluated** | | | | | |
| **0** | **1.15 [1.92, 1.43]** | **1.23 [1.05, 1.46]** | **1.46 [1.30, 1.64]** | **1.12 [1.01, 1.24]** | **1.21 [1.08, 1.34]** |
| **1-8** | Ref | Ref | Ref | Ref | Ref |
| **9-11** | **0.81 [0.71, 0.93]** | **0.89 [0.81, 0.98]** | **0.89 [0.83, 0.95]** | **0.86 [0.82, 0.91]** | **0.87 [0.82, 0.91]** |
| **12-15** | **0.79 [0.70, 0.91]** | **0.82 [0.75, 0.91]** | **0.81 [0.75, 0.87]** | **0.84 [0.80, 0.88]** | **0.83 [0.78, 0.87]** |
| **16-19** | **0.67 [0.57, 0.78]** | **0.73 [0.65, 0.82]** | **0.77 [0.71, 0.84]** | **0.71 [0.66, 0.76]** | **0.77 [0.72, 0.83]** |
| **20-29** | **0.66 [0.57, 0.75]** | **0.70 [0.63, 0.78]** | **0.75 [0.69, 0.82]** | **0.71 [0.66, 0.76]** | **0.74 [0.70, 0.79]** |
| **30-39** | **0.46 [0.37, 0.58]** | **0.67 [0.56, 0.81]** | **0.70 [0.60, 0.81]** | **0.66 [0.58, 0.75]** | **0.71 [0.62, 0.81]** |
| **≥40** | **0.60 [0.47, 0.76]** | **0.51 [0.39, 0.67]** | **0.68 [0.56, 0.82]** | **0.64 [0.54, 0.77]** | **0.69 [0.57, 0.83]** |

* Also adjusted for age, race, sex, tumor grade, tumor location, AJCC Stage, type of surgical resection, post-operative radiation, year of diagnosis and registry. Bold indicates $p<0.05$.

In this sensitivity analysis, we find that the relative association between lymph node evaluation and 5-year relative hazard of death remains relatively stable when patients are stratified by age when compared to the findings in Tables 6a and 6b. We continue to conclude that patients with more extensive lymph node evaluation have a significantly lower 5-year relative hazard of death compared with those who have few nodes evaluated.

**Appendix 4: Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models,**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death All Patients N=86,394 | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Negative Patients (AJCC Stage I and II) N=47,162 | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Positive Patients (AJCC Stage III and IV) N=39,232 |
|---|---|---|---|
| **≥12 Lymph Nodes Evaluated** | | | |
| **No** | Ref | Ref | Ref |
| **Yes** | **0.79 [0.77, 0.81]** | **0.73 [0.72, 0.76]** | **0.82 [0.80, 0.84]** |

**Alternative Category Groupings for Lymph Node Evaluation (N=86,394)**

* Also adjusted for age, race, sex, AJCC stage, tumor grade, tumor location, type of surgical resection, year of diagnosis and registry. Bold indicates $p<0.05$.

In this sensitivity analysis, we conclude that receiving adequate lymph node evaluation is also associated with lower 5-year relative hazard of death, as were the models evaluating lymph node evaluation in smaller groupings (Tables 6a and 6b).

**Appendix 5: Removal of Non-Significant Factors from Multivariate Logistic Regression Models Assessing the Association Between More Extensive Lymph Node Evaluation and Relative Odds of Node Positivity (N=83,671)**

The following results are the Wald chi-square tests of significance for the logistic regression model when all factors believed to confound the association between more extensive lymph node evaluation and odds of node positivity are included in the model. Patient sex is borderline significant.

Type 3 Analysis of Effects

| Effect | DF | Wald Chi-Square | Pr > ChiSq |
|---|---|---|---|
| LN Eval | 6 | 200.1665 | <.0001 |
| Age | 4 | 712.4850 | <.0001 |
| Race | 2 | 53.7257 | <.0001 |
| Sex | 1 | 3.6758 | 0.0552 |
| Tstage | 3 | 8280.5233 | <.0001 |
| Grade | 2 | 1402.8943 | <.0001 |
| Location | 2 | 23.2200 | <.0001 |
| Registry | 8 | 38.8364 | <.0001 |
| Surgery Type | 5 | 24.6471 | 0.0002 |
| Year of Dx | 6 | 87.3769 | <.0001 |

After removing patient sex from the multivariate model, we still conclude that more extensive lymph node evaluation is significantly associated with slightly higher relative odds of node positivity (see following page).

Type 3 Analysis of Effects with Age Removed

| Effect | DF | Wald Chi-Square | Pr > ChiSq |
|---|---|---|---|
| LN Eval | 6 | 199.4944 | <.0001 |
| Age | 4 | 734.6877 | <.0001 |
| Race | 2 | 52.9067 | <.0001 |
| Tstage | 3 | 8285.9164 | <.0001 |
| Grade | 2 | 1399.5994 | <.0001 |
| Location | 2 | 23.8327 | <.0001 |
| Registry | 8 | 38.9627 | <.0001 |
| Surgery Type | 5 | 25.6752 | 0.0001 |
| Year of Dx | 6 | 87.4937 | <.0001 |

**Appendix 5 (Continued): Removal of Non-Significant Factors from Multivariate Logistic Regression Models Assessing the Association Between More Extensive Lymph Node Evaluation and Relative Odds of Node Positivity (N=83,671)**

| | **Odds Ratios [95% Confidence Interval]** | |
|---|---|---|
| | Model 1 with Sex Included N=83,671 | Model 2 with Sex Removed N=83,671 |
| **Lymph Nodes Evaluated** | | |
| **1-8** | Ref | Ref |
| **9-11** | **1.28 [1.23, 1.34]** | **1.28 [1.23, 1.34]** |
| **12-15** | **1.29 [1.24, 1.35]** | **1.29 [1.23, 1.35]** |
| **16-19** | **1.28 [1.21, 1.34]** | **1.27 [1.21, 1.34]** |
| **20-29** | **1.19 [1.13, 1.24]** | **1.19 [1.13, 1.25]** |
| **30-39** | **1.11 [1.02, 1.20]** | **1.11 [1.02, 1.20]** |
| **≥40** | 1.06 [0.96, 1.18] | 1.06 [0.95, 1.18] |

* Also adjusted for age, race, T-stage, tumor grade, tumor location, type of surgical resection, year of diagnosis and registry. Bold indicates $p<0.05$.

**Appendix 6: Removal of Non-Significant Factors from Cox Proportional Hazards Models Assessing the Association Between More Extensive Lymph Node Evaluation and 5-year Relative Hazard of Death**

The following results are the Wald chi-square tests of significance for the Cox Proportional hazards regression model when all factors believed to confound the association between more extensive lymph node evaluation and 5-year relative hazard of death are included in the model. All factors are highly significant at $p<0.05$ and were kept in the final models.

**Model 1- All Patients (N=86,394)**

Type 3 Tests

| Effect | DF | Wald Chi-Square | Pr > ChiSq |
|---|---|---|---|
| LN Eval | 7 | 674.3048 | <.0001 |
| Age | 4 | 5722.1233 | <.0001 |
| Race | 2 | 114.7805 | <.0001 |
| Sex | 1 | 150.7413 | <.0001 |
| AJCC Stage | 3 | 24107.1559 | <.0001 |
| Grade | 2 | 620.9644 | <.0001 |
| Location | 2 | 187.1416 | <.0001 |
| Registry | 8 | 50.5949 | <.0001 |
| Surgery Type | 5 | 37.4303 | <.0001 |
| Post-op Rad | 1 | 39.0599 | <.0001 |
| Year of Dx | 6 | 354.0701 | <.0001 |

**Model 2- Node-Positive Patients (N=39,232)**

Type 3 Tests

| Effect | DF | Wald Chi-Square | Pr > ChiSq |
|---|---|---|---|
| LN Eval | 7 | 315.6796 | <.0001 |
| Age | 4 | 2153.2259 | <.0001 |
| Race | 2 | 43.3692 | <.0001 |
| Sex | 1 | 15.8060 | <.0001 |
| AJCC Stage | 1 | 9536.5600 | <.0001 |
| Grade | 2 | 677.6501 | <.0001 |
| Location | 2 | 241.0764 | <.0001 |
| Registry | 8 | 22.2093 | 0.0045 |
| Surgery Type | 5 | 34.7383 | <.0001 |
| Post-op Rad | 1 | 7.1311 | 0.0076 |
| Year of Dx | 6 | 388.9865 | <.0001 |

**Model 3- Node-Negative Patients (N=47,162)**

Type 3 Tests

| Effect | DF | Wald Chi-Square | Pr > ChiSq |
|---|---|---|---|
| LN Eval | 7 | 386.5905 | <.0001 |
| Age | 4 | 3944.8655 | <.0001 |
| Race | 2 | 101.9057 | <.0001 |
| Sex | 1 | 238.8329 | <.0001 |
| AJCC Stage | 1 | 606.6609 | <.0001 |
| Grade | 2 | 38.9852 | <.0001 |
| Location | 2 | 10.3176 | 0.0057 |
| Registry | 8 | 52.5623 | <.0001 |
| Surgery Type | 5 | 54.3556 | <.0001 |
| Post-op Rad | 1 | 63.8384 | <.0001 |
| Year of Dx | 6 | 36.8171 | <.0001 |

**Appendix 7: Association between Lymph Node Evaluation and 5-Year Relative Hazard of Death, Cox Proportional Hazards Models, Adjusting for Tumor Extent using T-Stage Instead of AJCC Stage**

| | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death All Patients N=86,394 | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Negative Patients | **Adjusted Hazard Ratio [95% Confidence Interval]** 5-Year Relative Hazard of Death Node Positive Patients |
|---|---|---|---|
| **Lymph Nodes Evaluated** | | | |
| **0** | **1.35 [1.28, 1.43]** | **1.23 [1.12, 1.34]** | **1.57 [1.46, 1.69]** |
| **1-8** | Ref | Ref | Ref |
| **9-11** | **0.86 [0.79, 0.84]** | **0.82 [0.78, 0.86]** | **0.87 [0.83, 0.90]** |
| **12-15** | **0.81 [0.71, 0.76]** | **0.78 [0.74, 0.83]** | **0.80 [0.77, 0.83]** |
| **16-19** | **0.73 [0.71, 0.76]** | **0.69 [0.64, 0.74]** | **0.73 [0.70, 0.77]** |
| **20-29** | **0.70 [0.67, 0.72]** | **0.64 [0.60, 0.69]** | **0.72 [0.68, 0.75]** |
| **30-39** | **0.61 [0.57, 0.66]** | **0.54 [0.48, 0.62]** | **0.65 [0.60, 0.71]** |
| **≥40** | **0.57 [0.52, 0.62]** | **0.52 [0.44, 0.62]** | **0.60 [0.54, 0.67]** |
| **T-Stage** | | | |
| **I** | Ref. | Ref. | Ref. |
| **II** | **1.45 [1.37, 1.56]** | **1.29 [1.20, 1.38]** | **1.46 [1.22, 1.74]** |
| **III** | **2.60 [2.46, 2.74]** | **1.83 [1.72, 1.95]** | **2.67 [2.28, 3.13]** |
| **IV** | **7.72 [7.31, 8.16]** | **2.73 [2.53, 2.93]** | **7.42 [6.33, 8.70]** |

* Also adjusted for age, race, sex, tumor grade, tumor location, type of surgical resection, post-operative radiation, year of diagnosis and registry. Bold indicates $p<0.05$. In this sensitivity analysis, we find that the relative hazard of death as more lymph nodes are evaluated is comparable to Tables 6a and 6b, which adjust for AJCC stage instead of T-stage. These findings indicate that the association between lymph node evaluation and relative hazard of death is stable across measures for tumor extent.

**Appendix 8: Chapter 4 Patient Inclusion Criteria Codes, Colon Cohort (N=17,906)**

| | |
|---|---|
| SEER Primary Site (ICD-O-3) | |
| C-180 | Cecum |
| C-182 | Ascending Colon |
| C-183 | Hepatic Flexure |
| C-184 | Transverse Colon |
| C-185 | Splenic Flexure |
| C-186 | Descending Colon |
| C-187 | Sigmoid Colon |
| SEER Tumor Histology (ICD-O-3) | |
| 8140-8149, 8210-8219, 8220-8229, 8260-8269, 8480-8489, 8570-8579 | Adenocarcinomas |
| AJCC (TNM) Stage, 6th Edition | |
| T1-4, N1-2, M0 | Stage III |
| SEER Surgery Codes- Radical Excision | |
| **1992-1997** | |
| 30 | Partial colectomy, but less than hemicolectomy |
| 40 | Hemicolectomy or greater (but less than total); right or left colectomy |
| 50 | Total Colectomy |
| 60 | Colectomy, NOS |
| 70 | Colectomy (subtotal, hemicolectomy or total) PLUS partial or total removal of other organs |
| **1998-2007** | |
| 30 | Partial colectomy, but less than hemicolectomy |
| 40 | Hemicolectomy or greater (but less than total); right or left colectomy |
| 50 | Total Colectomy |
| 60 | Total Proctocolectomy |
| 70 | Colectomy or coloproctectomy WITH and en bloc resection of other organs: pelvic exenteration |
| 80 | Colectomy, NOS |
| Hospitalization data (MedPAR) ICD-9 Surgery Codes | |
| 45.40-45.49 | Local excision or destruction of lesion or tissue of large intestine |
| 45.70-45.79 | Open and partial excision of large intestine |
| 45.80-45.89 | Total intra-abdominal colectomy |

ICD-O-3: International Classification of Diseases for Oncology, 3rd Revision; T=Extent of bowel wall penetration; N: Lymph Node Involvement; M: Metastases; ICD-9: International Classification of Diseases 9th Revision

**Appendix 9: Final Cohort, Surgically Treated AJCC Stage III Colon Cancer Patients in SEER-Medicare between 1992-2007 (N=17,906)**

| Inclusion Criteria | Number Excluded | Subtotal Remaining |
|---|---|---|
| Clinical and Treatment Inclusion Criteria (SEER) | | |
| Diagnosed with primary AJCC Stage IIII adenocarcinoma of the colon after age 66 between 1992-2007 (Appendix 1) | | 30,891 |
| Not diagnosed by autopsy or death certificate | 11 | 30,880 |
| Known Month of Diagnosis | 26 | 30,854 |
| No pre-operative radiation | 39 | 30,815 |
| Radical Excision Performed, according to SEER (Appendix 1) | 203 | 30,612 |
| Known number of lymph nodes surgically evaluated | 911 | 29,701 |
| Medicare Enrollment Inclusion Criteria | | |
| No HMO enrollment six months prior to 3 years post diagnosis | 7,684 | 22,017 |
| Enrolled in Medicare Part A + B six months prior to 3 years post diagnosis | 1,781 | 20,236 |
| Treatment Inclusion Criteria (Medicare Claims-based Evidence) | | |
| Hospitalization record for radical excision of the colon within six months of diagnosis | 1,547 | 18,689 |
| Only one Hospitalization record for radical excision within six months of diagnosis | 783 | 17,906 |
| **Final Cohort** | | **17,906** |

**Appendix 10: Chemotherapy Administration and Drug Codes Used to Identify Chemotherapy Receipt, by Type of Medicare File**

| | MedPAR Files | Outpatient Files | National Claims History (NCH) Files | Durable Medical Equipment Files (DME) |
|---|---|---|---|---|
| **ICD-9 Diagnosis Codes** | V58.1, V58.11, V58.12, V66.2, V67.2 | V58.1, V58.11, V58.12, V66.2, V67.2 | | |
| **ICD-9 Procedure Codes** | 99.25 | 99.25 | | |
| **CPT Procedure Codes (HCPCS)** | | **Administration:** 36260, 95990-95991, 96400-96549, Q0083-Q0085, G0355-G0362; **Agents:** C1167, C9127, C9414, C9425, C9427, C9431, C9432, C9440, C9205, C9214, C9215, C9257, C9418, E0782-E0786, G0355-G0362, J0207, J0640-J0641, J1190, J8520-J8521, J8530, J8650, J8565, J8600, J8700, J8999, J9000-J9999, Q2024, S0177 | **Administration:** 36260, 95990-95991, 96400-96549, Q0083-Q0085, G0355-G0362; **Agents:** C1167, C9127, C9414, C9425, C9427, C9431, C9432, C9440, C9205, C9214, C9215, C9257, C9418, E0782-E0786, G0355-G0362, J0207, J0640-J0641, J1190, J8520-J8521, J8530, J8650, J8565, J8600, J8700, J8999, J9000-J9999, Q2024, S0177 | |
| **Revenue Center Codes** | | 0331, 0332 | | |

**Appendix 10 (continued): Chemotherapy Administration and Drug Codes**

| | MedPAR Files | Outpatient Files | National Claims History (NCH) Files | Durable Medical Equipment Files (DME) |
|---|---|---|---|---|
| **NDC Codes** | | | | 4110013, 4110016, 4110020, 4110022, 4110051, 4110113, 4110116, 4110150, 4110151, 53808041101, 54868414301-03, 54868526001-09, 17101050301-02, 17101050401, 00179165270-72, 6049117001, 6049117028, 15050301, 378326694, 55567005002, 55361163904, 57423000104, 51079096501, 51079096505, 15309145, 85125901, 00085300101-02, 00085300401-02, 00085125201-02, 00085151901-02, 00085133601-02, 00085142501-02, 00085143001-02, 85141701, 54868535400, 54868414202-06, 54868534801, 53922151901-02, 53922136601-02, 53922300401-02, 53922141701, 53922143001-02, 53922142501-02, 11326124801-02, 11326124401-02, 11326125901-02, 11326125201-02, 51129309901,02, 17088005001, 17088003101, 17088004901, 66828003001, 00078040105,34, 78043815, 54868542700-03, 54868528900-04 |

## Appendix 11: Diagnosis and Procedure Codes Used to Determine Receipt of Post-Surgical Care, by Type of Medicare File

| Source | ICD-9 Procedure Codes | ICD-9 Diagnosis Codes | CPT Procedure Codes |
|---|---|---|---|
| ***Carcinoembyonic Antigen (CEA) test*** | | | |
| MedPAR Files | | 795.81 | |
| Outpatient Files | | 795.81 | 82378 |
| National Claims History (NCH) Files | | | 82378 |
| ***Computed tomography (CT) scan of the chest and abdomen*** | | | |
| MedPAR Files | 87.41, 88.01 | | |
| Outpatient Files | 87.41, 88.01 | | 74150, 74160, 74170, 71250, 71260, 71270 |
| National Claims History (NCH) Files | | | 74150, 74160, 74170, 71250, 71260, 71270 |
| ***Colonoscopy*** | | | |
| MedPAR Files | 45.23, 45.25, 45.42, 45.43 | V76.51 | |
| Outpatient Files | 45.23, 45.25, 45.42, 45.43 | V76.51 | G0105, G0121, 45378, 45379, 45381, 45382, 45383, 45384, 45385, 45386, 45387, 45391, 44388, 44389, 44390, 44391, 44392, 44393, 44394, 44397 |
| National Claims History (NCH) Files | | | G0105, G0121, 45378, 45379, 45381, 45382, 45383, 45384, 45385, 45386, 45387, 45391, 44388, 44389, 44390, 44391, 44392, 44393, 44394, 44397 |

**Appendix 12a: Predictors of Guideline Recommended Post-Surgical Care for AJCC Stage III Colon Cancer Patients, Alternate Category Groupings for Lymph Node Evaluation*, Adjusted Odds Ratio (95% CI)**

| | Chemotherapy Receipt within 6 Months of Diagnosis | | Colonoscopy within 3 Years of Surgical Treatment | |
|---|---|---|---|---|
| | **All Patients (N=17,906)** | **6 Month Survivors (N= 15, 581)** | **All Patients (N=17,906)** | **6 Month Survivors (N= 15, 581)** |
| **Lymph Nodes Evaluated** | | | | |
| **0** | **0.39 [0.16, 0.93]** | **0.46 [0.18, 1.25]** | **0.63 [0.27, 1.49]** | **0.62 [0.20, 1.88]** |
| **1-8** | Ref | Ref | Ref | Ref |
| **9-11** | **1.13 [1.02, 1.26]** | 1.11 [0.99, 1.25] | **1.12 [1.02, 1.24]** | 1.00 [0.87, 1.15] |
| **12-15** | 1.09 [0.99, 1.21] | 1.03 [0.92, 1.15] | **1.12 [1.02, 1.23]** | 1.00 [0.87, 1.14] |
| **16-19** | **1.15 [1.03, 1.30]** | 1.06 [0.94, 1.20] | **1.22 [1.09, 1.35]** | 0.99 [0.87, 1.14] |
| **20-29** | **1.21 [1.08, 1.36]** | 1.10 [0.97, 1.25] | **1.19 [1.07, 1.32]** | 0.96 [0.83, 1.11] |
| **30-39** | **1.24 [1.01, 1.51]** | 1.11 [0.89, 1.38] | **1.32 [1.10, 1.58]** | 1.07 [0.84, 1.39] |
| **≥40** | 1.01 [0.77, 1.33] | 0.87 [0.65, 1.17] | 1.09 [0.85, 1.39] | 0.73 [0.53, 1.01] |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, year of diagnosis and registry. Bold indicates $p<0.05$.

**Appendix 12b: Predictors of Guideline Recommended Post-Surgical Care for AJCC Stage III Colon Cancer Patients Alternate Category Groupings for Lymph Node Evaluation*, Adjusted Odds Ratio (95% CI)**

| | Computed Tomography (CT) Scan of the Chest or Abdomen within 3 Years of Surgical Treatment | | Carcinoembryonic Antigen (CEA) Test within 3 years of Surgical Treatment | |
|---|---|---|---|---|
| | **All Patients (N=17,906)** | **3 Year Survivors (N=10,016)** | **All Patients (N=17,906)** | **3 Year Survivors (N=10,016)** |
| **Lymph Nodes Evaluated** | | | | |
| **0** | **0.34 [0.15, 0.77]** | 0.44 [0.14, 1.40] | 0.54 [0.24, 1.19] | **0.46 [0.13, 1.61]** |
| **1-8** | Ref | Ref | Ref | Ref |
| **9-11** | 0.97 [0.88, 1.07] | 0.88 [0.77, 1.02] | **1.21 [1.09, 1.34]** | 1.06 [0.89, 1.28] |
| **12-15** | 1.04 [0.95, 1.15] | 0.95 [0.83, 1.09] | **1.19 [1.08, 1.32]** | 1.11 [0.93, 1.33] |
| **16-19** | 1.07 [0.96, 1.20] | 0.94 [0.81, 1.10] | **1.33 [1.18, 1.50]** | 1.06 [0.87, 1.30] |
| **20-29** | 0.98 [0.89, 1.10] | **0.80 [0.69, 0.93]** | **1.35 [1.19, 1.52]** | 1.15 [0.94, 1.41] |
| **30-39** | 1.16 [0.95, 1.41] | 1.08 [0.83, 1.41] | **1.70 [1.37, 2.13]** | 1.74 [1.15, 2.62] |
| **≥40** | 0.89 [0.69, 1.17] | 0.78 [0.55, 1.10] | **1.52 [1.12, 2.07]** | 1.64 [0.92, 2.92] |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, year of diagnosis and registry. Bold indicates $p<0.05$.
In this sensitivity analysis breaking the level of lymph node evaluation out into smaller groups, we continue to find that at the time of diagnosis, patients who received adequate lymph node evaluation were also more likely to receive recommended post-surgical care (adjuvant chemotherapy, CEA testing, and colonoscopy), with the exception CT scans. However, among patients who survived to the end of the eligibility period for post-surgical care, we found that individuals with adequate lymph node evaluation were no more likely to receive recommended post-surgical care than those with <12 nodes evaluated ($p>0.05$ for all).

**Appendix 13a: Predictors of Guideline Recommended Post-Surgical Care for AJCC Stage III Colon Cancer Patients, Alternate Timing for Receipt of Post-Surgical Care (Within 1 Year of Surgery)*, Adjusted Odds Ratio (95% CI)**

| | Chemotherapy Receipt within 1 Year of Diagnosis | | Colonoscopy within 1 Year of Surgical Treatment | |
|---|---|---|---|---|
| | **All Patients (N=17,906)** | **1 Year Survivors (N= 15, 581)** | **All Patients (N=17,906)** | **1 Year Survivors (N= 15, 581)** |
| **Lymph Nodes Evaluated** | | | | |
| **<12** | Ref | Ref | Ref | Ref |
| **≥12** | **1.07 [1.00, 1.15]** | 0.99 [0.91, 1.07] | **1.11 [1.04, 1.20]** | 1.06 [0.97, 1.15] |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, year of diagnosis and registry. Bold indicates $p<0.05$.

**Appendix 13b: Predictors of Guideline Recommended Post-Surgical Care for AJCC Stage III Colon Cancer Patients, Alternate Timing for Receipt of Post-Surgical Care (Within 1 Year of Surgery)*, Adjusted Odds Ratio (95% CI)**

| | Computed Tomography (CT) Scan of the Chest or Abdomen within 1 Year of Surgical Treatment | | Carcinoembryonic Antigen (CEA) Test within 1 year of Surgical Treatment | |
|---|---|---|---|---|
| | **All Patients (N=17,906)** | **1 Year Survivors (N=10,016)** | **All Patients (N=17,906)** | **1 Year Survivors (N=10,016)** |
| **Lymph Nodes Evaluated** | | | | |
| **<12** | Ref | Ref | Ref | Ref |
| **≥12** | 1.01 [0.95, 1.07] | 0.94 [0.88, 1.01] | **1.17 [1.10, 1.26]** | 1.09 [1.00, 1.18] |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, year of diagnosis and registry. Bold indicates p<0.05.

In this sensitivity analysis which evaluates receipt of post-surgical care within 1 year of surgery, we continue to find that at the time of diagnosis, patients who received adequate lymph node evaluation were also more likely to receive recommended post-surgical care (adjuvant chemotherapy, CEA testing, and colonoscopy), with the exception CT scans. However, among patients who survived to the end of the eligibility period for post-surgical care, we found that individuals with adequate lymph node evaluation were no more likely to receive recommended post-surgical care than those with <12 nodes evaluated (p>0.05 for all).

**Appendix 14a: Predictors of Guideline Recommended Post-Surgical Care for AJCC Stage III Colon Cancer Patients, Alternate Timing for Receipt of Post-Surgical Care (Within 5 Years of Surgery)*, Adjusted Odds Ratio (95% CI)**

| | **Chemotherapy Receipt within 5 Years of Diagnosis (N/A)** | | **Colonoscopy within 5 Years of Surgical Treatment** | |
|---|---|---|---|---|
| | **All Patients (N=17,906)** | **1 Year Survivors (N= 15, 581)** | **All Patients (N=17,906)** | **5 Year Survivors (N= 15, 581)** |
| **Lymph Nodes Evaluated** | | | | |
| **<12** | - | - | Ref | Ref |
| **≥12** | - | - | **1.13 [1.06, 1.21]** | 0.94 [0.83, 1.05] |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, year of diagnosis and registry. Bold indicates p<0.05.

**Appendix 14b: Predictors of Guideline Recommended Post-Surgical Care for AJCC Stage III Colon Cancer Patients, Alternate Timing for Receipt of Post-Surgical Care (Within 5 Years of Surgery)*, Adjusted Odds Ratio (95% CI)**

| | Computed Tomography (CT) Scan of the Chest or Abdomen within 5 Years of Surgical Treatment | | Carcinoembryonic Antigen (CEA) Test within 5 years of Surgical Treatment | |
|---|---|---|---|---|
| | **All Patients (N=17,906)** | **5 Year Survivors (N=10,016)** | **All Patients (N=17,906)** | **5 Year Survivors (N=10,016)** |
| **Lymph Nodes Evaluated** | | | | |
| **<12** | Ref | Ref | Ref | Ref |
| **≥12** | 1.02 [0.95, 1.09] | 0.92 [0.84, 1.00] | **1.21 [1.12, 1.30]** | 1.00 [1.00, 1.26] |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, year of diagnosis and registry. Bold indicates $p<0.05$.

In this sensitivity analysis which evaluates receipt of post-surgical care within 5 years of surgery, we continue to find that at the time of diagnosis, patients who received adequate lymph node evaluation were also more likely to receive recommended post-surgical care (CEA testing and colonoscopy), with the exception CT scans. Receipt of adjuvant chemotherapy was not assessed as recommendations all fall within 1 year of diagnosis. However, among patients who survived to the end of the eligibility period for post-surgical care, we found that individuals with adequate lymph node evaluation were no more likely to receive recommended post-surgical care than those with <12 nodes evaluated ($p>0.05$ for all).

**Appendix 15: Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Logistic Regression Models Evaluating the Association between Lymph Node Evaluation and Receipt of Post-Surgical Care**

The following sensitivity analyses evaluate the presence of a significant interaction between the level of lymph node evaluation a patient receives and other characteristics of those patients. Specifically, we assessed whether a significant interaction was present between the level of lymph node evaluation and patient age, race, sex, t-stage, and tumor grade. A significant interaction would indicate that the association between lymph node evaluation and receipt of post-surgical care varied by one or multiple of these patient characteristics. We used the likelihood ratio test to evaluate the presence of a significant interaction in our models.[84] The likelihood ratio test uses the ratio of the maximized value of the likelihood function for the interaction model (L1) over the maximized value of the likelihood function for the full model (L0). The likelihood test statistic equals:

$$-2\log\left(\frac{L_0}{L_1}\right) = -2[\log(L_0) - \log(L_1)] = -2(L_0 - L_1)$$

This log transformation of the likelihood function yields a chi-square statistic. We considered a p-value for this chi-square statistic of <0.05 to be significant.

For all interaction analyses, the Full model indicates a logistic regression model evaluating the association between lymph node evaluation and receipt of post-surgical care, adjusting for patient age, race, sex, T-stage, tumor grade, tumor location, Charlson score, year of diagnosis and registry.

**Receipt of Chemotherapy within 6 months of Diagnosis (N=17,906)**

LN Evaluation*Age Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 19576.23 | 4 | >0.25 |
| Full Model + Interaction term between LN Evaluation*age (L1) | 19571.82 | | |
| Difference | 4.41 | | |

LN Evaluation*Race Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 19576.23 | 2 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Race (L1) | 19575.29 | | |
| Difference | 0.94 | | |

**Appendix 15 (Continued): Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Logistic Regression Model Evaluating the Association between Lymph Node Evaluation and Receipt of Post-Surgical Care**

**Receipt of Chemotherapy within 6 months of Diagnosis (N=17,906)**

LN Evaluation*Sex Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 19576.23 | 1 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Sex (L1) | 19576.16 | | |
| Difference | 0.07 | | |

LN Evaluation*T-stage Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 19576.23 | 3 | >0.25 |
| Full Model + Interaction term between LN Evaluation*T-stage (L1) | 19573.75 | | |
| Difference | 2.48 | | |

LN Evaluation*Charlson Score Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 19576.23 | 3 | 0.10 |
| Full Model + Interaction term between LN Evaluation*Tumor Grade (L1) | 19569.86 | | |
| Difference | 6.37 | | |

**Appendix 15 (Continued): Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Logistic Regression Model Evaluating the Association between Lymph Node Evaluation and Receipt of Post-Surgical Care**

**Colonoscopy within 3 Years of Surgical Treatment (N=17,906)**

LN Evaluation*Age Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 22400.86 | 4 | 0.25 |
| Full Model + Interaction term between LN Evaluation*age (L1) | 22395.02 | | |
| Difference | 5.84 | | |

LN Evaluation*Race Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 22400.86 | 2 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Race (L1) | 22400.15 | | |
| Difference | 0.71 | | |

LN Evaluation*Sex Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 22400.86 | 1 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Sex (L1) | 22400.85 | | |
| Difference | 0.01 | | |

LN Evaluation*T-stage Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 22400.86 | 3 | >0.25 |
| Full Model + Interaction term between LN Evaluation*T-stage (L1) | 22397.38 | | |
| Difference | 3.48 | | |

**Appendix 15 (Continued): Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Logistic Regression Model Evaluating the Association between Lymph Node Evaluation and Receipt of Post-Surgical Care**

**Colonoscopy within 3 Years of Surgical Treatment (N=17,906)**

LN Evaluation*Charlson Score Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 22400.86 | 3 | 0.25 |
| Full Model + Interaction term between LN Evaluation*Tumor Grade (L1) | 22396.69 | | |
| Difference | 4.17 | | |

**CT Scan within 3 Years of Surgical Treatment (N=17,906)**

LN Evaluation*Age Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 20949.44 | 4 | >0.25 |
| Full Model + Interaction term between LN Evaluation*age (L1) | 20947.39 | | |
| Difference | 2.05 | | |

LN Evaluation*Race Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 20949.44 | 2 | 0.20 |
| Full Model + Interaction term between LN Evaluation*Race (L1) | 20946.22 | | |
| Difference | 3.22 | | |

LN Evaluation*Sex Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 20949.44 | 1 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Sex (L1) | 20949.00 | | |
| Difference | 0.44 | | |

**Appendix 15 (Continued): Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Logistic Regression Model Evaluating the Association between Lymph Node Evaluation and Receipt of Post-Surgical Care**

**CT Scan within 3 Years of Surgical Treatment (N=17,906)**

LN Evaluation*T-stage Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 20949.44 | 3 | 0.20 |
| Full Model + Interaction term between LN Evaluation*T-stage (L1) | 20944.60 | | |
| Difference | 4.8 | | |

LN Evaluation*Charlson Score Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 20949.44 | 3 | 0.20 |
| Full Model + Interaction term between LN Evaluation*Tumor Grade (L1) | 20944.58 | | |
| Difference | 4.78 | | |

**CEA Test within 3 Years of Surgical Treatment (N=17,906)**

LN Evaluation*Age Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 18746.69 | 4 | >0.25 |
| Full Model + Interaction term between LN Evaluation*age (L1) | 18743.87 | | |
| Difference | 2.82 | | |

LN Evaluation*Race Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 18746.69 | 2 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Race (L1) | 18744.59 | | |
| Difference | 2.1 | | |

**Appendix 15 (Continued): Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Logistic Regression Model Evaluating the Association between Lymph Node Evaluation and Receipt of Post-Surgical Care**

**CEA Test within 3 Years of Surgical Treatment (N=17,906)**

LN Evaluation*Sex Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 18746.69 | 1 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Sex (L1) | 18745.88 | | |
| Difference | 0.81 | | |

LN Evaluation*T-stage Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 18746.69 | 3 | 0.10 |
| Full Model + Interaction term between LN Evaluation*T-stage (L1) | 18740.52 | | |
| Difference | 6.17 | | |

LN Evaluation*Charlson Score Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 18746.69 | 3 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Tumor Grade (L1) | 18742.81 | | |
| Difference | 3.88 | | |

The interaction terms for LN Evaluation and age, race, sex and T-stage and Charlson score were all non-significant for models assessing the association between the level of lymph node evaluation and receipt of chemotherapy, colonoscopy, CT scans and CEA testing. These sensitivity analyses indicate that the relationship between lymph node evaluation and receipt of post-surgical care is consistent across the patient factors evaluated. Therefore, our conclusions about the relationship between lymph node evaluation and receipt of post-surgical care remain unchanged.

**Appendix 16: Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Cox Proportional Hazards Model Evaluating the Association between Lymph Node Evaluation and 10-Year Relative Hazard of Death (N=17,906)**

The following sensitivity analyses evaluate the presence of a significant interaction between the level of lymph node evaluation a patient receives and other characteristics of those patients. Specifically, we assessed whether a significant interaction was present between the level of lymph node evaluation and patient age, race, sex, t-stage, and tumor grade. A significant interaction would indicate that the association between lymph node evaluation and 10-year relative hazard of death varied by one or multiple of these patient characteristics. We used the likelihood ratio test to evaluate the presence of a significant interaction in our models.[84] The likelihood ratio test uses the ratio of the maximized value of the likelihood function for the interaction model (L1) over the maximized value of the likelihood function for the full model (L0). The likelihood test statistic equals:

$$-2\log\left(\frac{L_0}{L_1}\right) = -2[\log(L_0) - \log(L_1)] = -2(L_0 - L_1)$$

This log transformation of the likelihood function yields a chi-square statistic. We considered a p-value for this chi-square statistic of <0.05 to be significant.

For all interaction analyses, the Full model indicates a logistic regression model evaluating the association between lymph node evaluation and 10-year relative hazard of death, adjusting for patient age, race, sex, T-stage, tumor grade, tumor location, Charlson score, year of diagnosis, registry, receipt of chemotherapy, receipt of colonoscopy, receipt of CT scans, and receipt of CEA testing.

LN Evaluation*Age Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 213557.92 | 4 | 0.25 |
| Full Model + Interaction term between LN Evaluation*age (L1) | 213552.25 | | |
| Difference | 5.67 | | |

LN Evaluation*Race Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 213557.92 | 2 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Race (L1) | 213557.60 | | |
| Difference | 0.32 | | |

**Appendix 16 (continued): Interaction Analyses between the Level of Lymph Node Evaluation and Patient Factors, Cox Proportional Hazards Model Evaluating the Association between Lymph Node Evaluation and 10-Year Relative Hazard of Death**

LN Evaluation*Sex Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 213557.92 | 1 | >0.25 |
| Full Model + Interaction term between LN Evaluation*Sex (L1) | 213557.51 | | |
| Difference | 0.41 | | |

LN Evaluation*T-stage Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 213557.92 | 3 | >0.25 |
| Full Model + Interaction term between LN Evaluation*T-stage (L1) | 213557.24 | | |
| Difference | 0.64 | | |

LN Evaluation*Charlson Score Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 213557.92 | 3 | 0.25 |
| Full Model + Interaction term between LN Evaluation*Tumor Grade (L1) | 213553.47 | | |
| Difference | 4.45 | | |

The interaction terms for LN Evaluation and age, race, sex and T-stage and Charlson score were all non-significant for models assessing the association between the level of lymph node evaluation and 10-year relative hazard of death. These sensitivity analyses indicate that the relationship between lymph node evaluation and 10-year hazard of death is consistent across the patient factors evaluated. Therefore, our conclusions about the relationship between lymph node evaluation and 10-year relative hazard of death remain unchanged.

**Appendix 17: Unadjusted Association between the Number of Lymph Nodes Evaluated and the Number of Positive Lymph Nodes Identified Among AJCC Stage III Colon Cancer Patients, %* (N) (N=17,906)**

| | Number of Lymph Nodes Evaluated | |
|---|---|---|
| **Tumor N Category** | **<12 LNs Evaluated** | **≥12 LNs Evaluated** |
| N1 (1-3 Positive Nodes) | 74.9 (6,268) | 62.2 (5,931) |
| N2 (≥4 Positive Nodes) | 23.7 (1,987) | 37.0 (3,531) |
| Nx (Incomplete Information) | 1.4 (119) | 0.7 (70) |

*p<0.001; N1: Cancer cells found in 1-3 nearby lymph nodes; N2: Cancer cells found in ≥4 nearby lymph nodes; Nx: Incomplete information on the number of positive nodes[53]

In this sensitivity analysis, we find that the number of positive lymph nodes identified is associated with the number of lymph nodes evaluated.

**Appendix 18: Association between the Number of Positive Lymph Nodes Identified and Receipt of Post-Surgical Care Among AJCC Stage III Colon Cancer Patients, * Adjusted Odds Ratio (95% CI) with the Number of Positive Nodes Included % (N) (N=17,906)**

| | Chemotherapy Receipt within 6 Months of Diagnosis | | Colonoscopy within 3 Years of Surgical Treatment | |
|---|---|---|---|---|
| | **All Patients (N=17,906)** | **6 Month Survivors (N= 15, 581)** | **All Patients (N=17,906)** | **6 Month Survivors (N= 15, 581)** |
| **Number of Positive Lymph Nodes** | | | | |
| **N1 (1-3 Positive Nodes)** | Ref | Ref | Ref | Ref |
| **N2 (≥4 Positive Nodes)** | 1.25 [1.16, 1.35] | 1.44 [1.32, 1.57] | 0.70 [0.66, 0.75] | 0.99 [0.89, 1.10] |
| **Nx (Incomplete Information)** | 0.21 [0.14, 0.30] | 0.18 [0.12, 0.28] | 0.89 [0.66, 1.22] | 0.73 [0.51, 1.06] |
| **Lymph Nodes Evaluated** | | | | |
| **<12** | Ref | Ref | Ref | Ref |
| **≥12** | 1.05 [0.98, 1.13] | 0.96 [0.88, 1.04] | 1.17 [1.09, 1.25] | 0.98, [0.73, 1.31] |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, Charlson score, year of diagnosis and registry. Bold indicates $p<0.05$.
N1: Cancer cells found in 1-3 nearby lymph nodes; N2: Cancer cells found in ≥4 nearby lymph nodes; Nx: Incomplete information on the number of positive nodes[53]

**Appendix 18(Continued): Association between the Number of Positive Lymph Nodes Identified and Receipt of Post-Surgical Care Among AJCC Stage III Colon Cancer Patients, * Adjusted Odds Ratio (95% CI) with the Number of Positive Nodes Included % (N) (N=17,906)**

| | Computed Tomography (CT) Scan of the Chest or Abdomen within 3 Years of Surgical Treatment | | Carcinoembryonic Antigen (CEA) Test within 3 years of Surgical Treatment | |
|---|---|---|---|---|
| | **All Patients (N=17,906)** | **3 Year Survivors (N=10,016)** | **All Patients (N=17,906)** | **3 Year Survivors (N=10,016)** |
| **Number of Positive Lymph Nodes** | | | | |
| **N1 (1-3 Positive Nodes)** | Ref | Ref | Ref | Ref |
| **N2 (≥4 Positive Nodes)** | 1.26 [1.17, 1.36] | 1.37 [1.23, 1.54] | 0.95 [0.88, 1.03] | 1.31 [1.12, 1.53] |
| **Nx (Incomplete Information)** | 0.51 [0.38, 0.70] | 0.43 [0.30, 0.61] | 0.56 [0.41, 0.78] | 0.36 [0.24, 0.54] |
| **Lymph Nodes Evaluated** | | | | |
| **<12** | Ref | Ref | Ref | Ref |
| **≥12** | 1.02 [0.95, 1.09] | 0.92 [0.83, 1.01] | 1.21 [1.13, 1.31] | 1.08, [0.95, 2.06] |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, Charlson score, year of diagnosis and registry. Bold indicates $p<0.05$. N1: Cancer cells found in 1-3 nearby lymph nodes; N2: Cancer cells found in ≥4 nearby lymph nodes; Nx: Incomplete information on the number of positive nodes[53]

In this sensitivity analysis, we found that the number of positive nodes identified is associated with receiving chemotherapy, CT scans and CEA testing, but not colonoscopy. However, when we adjust for the number of positive nodes identified from a patient, our conclusions about the association between more extensive lymph node evaluation and receipt of post-surgical care do not change.

**Appendix 19: Factors Associated with 10-Year Relative Hazard of Death Among AJCC Stage III Colon Cancer Patients, Cox Proportional Hazard Models, Hazard Ratio Adjusting for Number of Positive Nodes, 95% CI**

| | **All Patients (N=17,906)** | | **3-Year Survivors (N=10, 016)** | |
|---|---|---|---|---|
| | Model 1 | Model 2 | Model 3 | Model 4 |
| **Lymph Nodes Evaluated** | | | | |
| <12 | Ref | Ref | Ref | Ref |
| ≥12 | 0.82 (0.79, 0.85) | 0.83 (0.80, 0.86) | 0.91 (0.86, 0.97) | 0.91 (0.85, 0.97) |
| **Number of Positive Lymph Nodes** | | | | |
| N1 | Ref | Ref | Ref | Ref |
| N2 | 1.53 (1.47, 1.59) | 1.56 (1.50, 1.62) | 1.29 (1.20, 1.39) | 1.31 (1.21, 1.41) |
| Nx | 0.70(0.57, 0.86) | 0.61 (0.50, 0.75) | 0.83(0.62, 1.12) | 0.77 (0.57, 1.04) |
| Guideline Recommended Post-Surgical Care | | | | |
| Chemotherapy within 6 months of diagnosis | | 0.78 (0.74, 0.82) | | 0.71 (0.65, 0.77) |
| Colonoscopy within 3 years of surgery | | 0.42 (0.40, 0.44) | | 0.68 (0.64, 0.74) |
| CT scan within 3 years of surgery | | 1.27 (1.22, 1.32) | | 1.57 (1.45, 1.69) |
| CEA within 3 years of surgery | | 0.49 (0.47, 0.51) | | 0.83 (0.76, 0.92) |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, Charlson score, year of diagnosis and registry. Bold indicates p<0.05.
N1: Cancer cells found in 1-3 nearby lymph nodes; N2: Cancer cells found in ≥4 nearby lymph nodes; Nx: Incomplete information on the number of positive nodes[53]

In this sensitivity analysis, we found that the number of positive nodes identified is associated with 10-year relative hazard of death among all patients and 3-year survivors. However, when we adjust for the number of positive nodes identified from a patient, our conclusions about the association between more extensive lymph node evaluation and 10-year relative hazard of death remain unchanged.

**Appendix 20: Factors Associated with 10-Year Relative Hazard of Death Among AJCC Stage III Colon Cancer Patients, Cox Proportional Hazard Models, Hazard Ratio Adjusting for Each Type of Post-Surgical Care Separately, 95% CI**

| | All Patients (N=17,906) | | | |
|---|---|---|---|---|
| | Model 1 | Model 2 | Model 3 | Model 4 |
| **Lymph Nodes Evaluated** | | | | |
| <12 | Ref | Ref | Ref | Ref |
| ≥12 | 0.85 (0.82, 0.89) | 0.86 (0.83, 0.89) | 0.86 (0.82, 0.88) | 0.88 (0.85, 0.91) |
| Guideline Recommended Post-Surgical Care | | | | |
| Chemotherapy within 6 months of diagnosis | 0.50 (0.48, 0.52) | | | |
| Colonoscopy within 3 years of surgery | | 0.34 (0.33, 0.35) | | |
| CT scan within 3 years of surgery | | | 0.86 (0.83, 0.89) | |
| CEA within 3 years of surgery | | | | 0.37 (0.35, 0.38) |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, Charlson score, year of diagnosis and registry. Bold indicates p<0.05.
In this sensitivity analysis, we find that the association between the level of lymph node evaluation and 10-year relative hazard of death remains consistent when the model is adjusted for each type of post-surgical care separately. However, we do find that the relationship between receipt of CT scans and 10-year relative hazard of death changes direction when all types of post-surgical care are included in the model (see Table 11). We, therefore conducted additional sensitivity analyses to evaluate potential interactions between receipt of CT scans and other patient factors (see appendix 21).

**Appendix 21: Interaction analyses between Receipt of CT Scans and Charlson Score on 10-Year Relative Hazard of Death Among AJCC Stage III Colon Cancer Patients, Cox Proportional Hazards Model 95% CI**

The following sensitivity analysis evaluate the presence of a significant interaction between receipt of CT scans and patient factors when assessing the association between receipt of CT scans and 10-year relative hazard of death. See Appendix 16 for a more complete description of how the interaction analyses were performed. Specifically, we evaluated whether an interaction was present between receipt of CT scans and a patient's age, race, sex, T-stage and Charlson score. We only found a significant interaction between receipt of CT scans and a patient's charlson comorbidity score (below) and, therefore, evaluated the association between lymph node evaluation and receipt of post-surgical care on 10-year relative hazard of death stratified by patients' comorbidity scores (See Appendix 22).

Receipt of CT Scans within 3-Years of Surgery*Charlson Score Interaction

| | -2 Log Likelihood | Degrees of Freedom | P-value |
|---|---|---|---|
| Full Model (L0) | 213557.92 | 3 | <0.001 |
| Full Model + Interaction term between LN Evaluation*Tumor Grade (L1) | 213480.19 | | |
| Difference | 77.7 | | |

**Appendix 22: Association between Lymph Node Evaluation and Receipt of Post-Surgical Care on 10-Year Relative Hazard of Death Among AJCC Stage III Colon Cancer Patients, Cox Proportional Hazards Model 95% CI**

| | Charlson Score=0 | Charlson Score=1 | Charlson Score=2 | Charlson Score=3 |
|---|---|---|---|---|
| **Number of Patients** | 11,178 | 3,193 | 1,694 | 1,841 |
| **Lymph Nodes Evaluated** | | | | |
| <12 | Ref | Ref | Ref | Ref |
| ≥12 | 0.86 (0.82, 0.91) | 0.88 (0.81, 0.97) | 1.00 (0.90, 1.15) | 0.92 (0.83, 1.03) |
| Guideline Recommended Post-Surgical Care | | | | |
| Chemotherapy within 6 months of diagnosis | 0.80 (0.79, 0.92) | 0.80 (0.69, 0.93) | 0.76 (0.68, 0.85) | 0.82 (0.77, 0.87) |
| Colonoscopy within 3 years of surgery | 0.46 (0.40, 0.52) | 0.41 (0.36, 0.47) | 0.45 (0.41, 0.50) | 0.38 (0.36, 0.40) |
| CT scan within 3 years of surgery | 0.83 (0.73, 0.93) | 1.07 (0.94, 1.22) | 1.22 (1.10, 1.34) | 1.53 (1.45, 1.63) |
| CEA within 3 years of surgery | 0.49 (0.43, 0.56) | 0.52 (0.44, 0.60) | 0.45 (0.41, 0.50) | 0.49 (0.46, 0.53) |

* Also adjusted for age, sex, race, T-stage, tumor grade, tumor location, year of diagnosis and registry. Bold indicates $p<0.05$.
In this sensitivity analysis, we find that the association between the level of lymph node evaluation and 10-year relative hazard of death remains consistent when the model is adjusted for each type of post-surgical care separately. However, we do find that the relationship between receipt of CT scans and 10-year relative hazard of death changes direction when we stratify our models by patients' Charlson score (see Table 11). Specifically, we find that among healthier patients (Charlson score=0), receipt of each type of post-surgical care is associated (See following page)
**Appendix 22 (Continued)**

(Continued from previous page) … with lower 10-year relative hazard of death. However, as the number of comorbidities patients' have increases, receipt of CT scans becomes associated with higher 10-year relative hazard of death. Because we do not know the reason for the CT scan (surveillance or symptom-driven), it's possible these patients have other competing illness or reduced immune system response that may be associated with higher likelihood of death that is not measured in our model. However, under all assumptions, the relative association between lymph node evaluation and 10-year hazard of death remains unchanged.

**Appendix 23: Chapter 5 Patient and Hospital Inclusion Criteria**

| Inclusion Criteria | Number of Patients Excluded | Subtotal Remaining (Patients) | Subtotal Remaining (Hospitals) |
|---|---|---|---|
| Clinical and Treatment Inclusion Criteria (SEER) | | | |
| Diagnosed with a first primary AJCC Stage I-IIII adenocarcinoma of the colon between 1992-2007 (Appendix B) in Registries reporting cases from 1992-2007 | | 54,003 | N/A |
| Over age 66 at diagnosis according to SEER and Medicare | 1,944 | 52,059 | N/A |
| Not diagnosed by autopsy or death certificate | 47 | 52,012 | N/A |
| Known Month of Diagnosis | 46 | 51,966 | N/A |
| No pre-operative radiation | 49 | 51,917 | N/A |
| Radical Exision Performed, according to SEER (Appendix B) | 3,052 | 48,865 | N/A |
| Known number of lymph nodes surgically evaluated | 935 | 47,930 | N/A |
| Medicare Enrollment Inclusion Criteria | | | |
| Enrolled in Medicare Part A + B six months prior to six months post diagnosis | 2,817 | 45,113 | N/A |
| No HMO enrollment six months prior to six months post diagnosis | 12,271 | 32,842 | N/A |

(Continued on the following page)

**Appendix 23 (Continued): Chapter 5 Patient and Hospital Inclusion Criteria**

| | | | |
|---|---|---|---|
| Treatment Inclusion Criteria (Medicare Claims-based Evidence) | | | |
| Hospitalization record for radical excision of the colon within six months of diagnosis | 2,981 | 29,861 | 695 |
| Only one Hospitalization record for radical excision within six months of diagnosis | 821 | 29,040 | 686 |
| Hospital Inclusion Criteria | | | |
| Treated in a hospital present in the Medicare data from 1992-2007 | 1,182 | 27,858 | 381 |
| Hospitals had at least 6 surgeries during each study period (i.e. performing approximately 2 per year) | 2,932 | 24,926 | 228 |

**Appendix 24: Hospital Factors associated with Improvement or Maintenance of Adequate Lymph Node Evaluation (i.e. Median LN Evaluation ≥11), Odds Ratios (95% CI)***

| | Short-Term (1999-2001 vs. 1996-1998) | Medium-Term (2002-2004 vs. 1996-1998) | Long-Term (2005-2007 vs. 1996-1998) |
|---|---|---|---|
| **Initial Median LN Evaluation ≥11 (1996-1998)** | Ref. | Ref. | Ref. |
| **Yes** | 6.26 (2.95, 13.28)* | 2.66 (1.32, 5.37)* | 2.13 (0.91, 4.98) |
| **Teaching Hospital** | | | |
| No | Ref. | Ref. | Ref. |
| Yes | 0.91 (0.39, 2.13) | 1.08 (0.50, 2.34) | 0.89 (0.37, 2.11) |
| **Hospital Ownership** | | | |
| Non-Profit | Ref. | Ref. | Ref. |
| For-Profit | 0.73 (0.24, 2.24) | 0.37 (0.13, 1.09) | 0.61 (0.21, 1.84) |
| Government | 1.19 (0.46, 3.11) | 1.58 (0.65, 3.84) | 1.64 (0.59, 4.55) |
| **Hospital Volume 1996-1998 (Quartiles)** | | | |
| 1 (6-13 procedures) | Ref. | Ref. | Ref. |
| 2 ( 14-21 procedures) | 0.79 (0.30, 2.08) | 2.28 (0.93, 5.61) | 1.60 (0.62, 4.13) |
| 3 (22-37 procedures) | 0.75 (0.27, 2.04) | 2.77 (1.06, 7.21) | 1.28 (0.46, 3.55) |
| 4 (≥38 procedures) | 0.95 (0.29, 3.04) | 0.67 (0.22, 2.10) | 2.17 (0.55, 8.70) |
| **Hospital Location** | | | |
| Rural | Ref. | Ref. | Ref. |
| Urban | 2.95 (0.99, 7.92) | 2.41 (1.03, 5.60) | 2.75 (1.12, 6.77) |
| **ACOSOG Member (Assessed in 2002)** | | | |
| No | Ref. | Ref. | Ref. |
| Yes | 1.37 (0.52, 3.62) | 1.92 (0.69, 5.35) | 2.05 (0.50, 8.52) |
| **C-Statistic** | 0.83 | 0.78 | 0.78 |

*Also Adjusted for Hospital-Level patient factors including: % of patients ≥80 years of age, % non-white patients, % of male patients, % of proximal tumors, % of high grade tumors, % of patients with a high Charlson score (≥3), % high staged (AJCC Stage III) cancers treated by the hospital.

| | | | |
|---|---|---|---|
| **Number of Patients** | 10,605 | 12,899 | 11,820 |
| **Number of Hospitals** | 228 | 228 | 228 |

**Appendix 25: Hospital Factors associated with Improvement or Maintenance of Adequate Lymph Node Evaluation (i.e. Median LN Evaluation ≥13), Odds Ratios (95% CI)***

| | Short-Term (1999-2001 vs. 1996-1998) | | Medium-Term (2002-2004 vs. 1996-1998) | | Long-Term (2005-2007 vs. 1996-1998) | |
|---|---|---|---|---|---|---|
| **Initial Median LN Evaluation ≥13 (1996-1998)** | Ref. | | Ref. | | Ref. | |
| **Yes** | 3.99 | (1.68, 9.53)* | 3.16 | (1.42, 7.04)* | 1.85 | (0.79, 4.35) |
| **Teaching Hospital** | | | | | | |
| No | Ref. | | Ref. | | Ref. | |
| Yes | 1.71 | (0.60, 4.94) | 1.26 | (0.54, 2.93) | 0.91 | (0.44, 1.90) |
| **Hospital Ownership** | | | | | | |
| Non-Profit | Ref. | | Ref. | | Ref. | |
| For-Profit | 0.54 | (0.11, 2.73) | 0.62 | (0.20, 1.91) | 1.63 | (0.60, 4.45) |
| Government | 0.70 | (0.20, 2.41) | 1.16 | (0.45, 2.94) | 1.12 | (0.49, 2.55) |
| **Hospital Volume 1996-1998 (Quartiles)** | | | | | | |
| 1 (6-13 procedures) | Ref. | | Ref. | | Ref. | |
| 2 ( 14-21 procedures) | 0.77 | (0.21, 2.75) | 2.69 | (0.98, 7.37) | 1.47 | (0.64, 3.38) |
| 3 (22-37 procedures) | 0.94 | (0.27, 3.31) | 2.41 | (0.84, 6.96) | 1.33 | (0.55, 3.17) |
| 4 (≥38 procedures) | 1.29 | (0.32, 5.16) | 1.18 | (0.36, 3.91) | 1.36 | (0.45, 4.09) |
| **Hospital Location** | | | | | | |
| Rural | Ref. | | Ref. | | Ref. | |
| Urban | 1.26 | (0.40, 4.04) | 2.31 | (0.91, 5.87) | 1.43 | (0.65, 3.13) |
| **ACOSOG Member (Assessed in 2002)** | | | | | | |
| No | Ref. | | Ref. | | Ref. | |
| Yes | 3.10 | (1.12, 8.55)* | 3.05 | (1.22, 7.59)* | 2.46 | (0.85, 7.16) |
| **C-Statistic** | 0.81 | | 0.79 | | 0.74 | |

*Also Adjusted for Hospital-Level patient factors including: % of patients ≥80 years of age, % non-white patients, % of male patients, % of proximal tumors, % of high grade tumors, % of patients with a high Charlson score (≥3), % high staged (AJCC Stage III) cancers treated by the hospital.

| | | | |
|---|---|---|---|
| **Number of Patients** | 10,605 | 12,899 | 11,820 |
| **Number of Hospitals** | 228 | 228 | 228 |